

# EXHIBIT 1



**FDA'S OVERSIGHT OF NECC AND AMERIDOSE:  
A HISTORY OF MISSED OPPORTUNITIES?**

**PRELIMINARY MAJORITY STAFF REPORT**

**COMMITTEE ON ENERGY AND COMMERCE**

**U.S. HOUSE OF REPRESENTATIVES  
113<sup>TH</sup> CONGRESS**

**APRIL 16, 2013**

## Table of Contents

Table of Contents.....	i
Table of Names and Abbreviations.....	ii
PART I: INTRODUCTION.....	1
PART II: FDA AUTHORITY OVER PHARMACY COMPOUNDING.....	4
PART III: FDA'S OVERSIGHT OF NECC: 2003-2006.....	7
A. <i>FDA is on Notice that NECC is Operating Outside the Scope of a Traditional Compounding Pharmacy.</i> .....	8
B. <i>After Issuing the 2006 Warning Letter to NECC, FDA Receives More Complaints About NECC Products and Practices.....</i>	11
C. <i>After Closing Out the 2006 Warning Letter, FDA Continues to Receive New Complaints About the Safety of NECC Products and the Company's Practices .....</i>	18
PART IV: OVERSIGHT OF NECC'S SISTER COMPANY, AMERIDOSE: 2006 – 2012 .....	21
A. <i>After Two Inspections Reveal Problems at Ameridose, FDA's Plan to Issue a Warning Letter to the Company is Ultimately Rejected.</i> .....	21
B. <i>From 2009-2012, FDA Fails to Take Action While Complaints about Ameridose's Products and Practices Continue to Mount.....</i>	27
C. <i>Despite an Increasing Number of Complaints, FDA Decides to Further Delay Action against Ameridose until after New 503A Guidance is Drafted.....</i>	32
PART V: CONCLUSION.....	39

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**FDA Office Abbreviations**

Center for Drug Evaluation and Research (CDER)  
Division of New Drugs and Labeling Compliance (DNDLC)  
Office of Regulatory Affairs (ORA)  
New England District Office (NWE-DO)  
Office of the Chief Counsel (OCC)  
Office of Criminal Investigations (OCI)

**State of Massachusetts Office Abbreviations**

Massachusetts Department of Public Health (MDPH)  
Massachusetts Board of Registration in Pharmacy (MBP)

**PRELIMINARY STAFF REPORT**  
**FDA'S OVERSIGHT OF NECC AND AMERIDOSE: A HISTORY OF MISSED**  
**OPPORTUNITIES?**

**PART I: INTRODUCTION**

In the summer and fall of 2012, a Massachusetts company, the New England Compounding Center (NECC), shipped over 17,000 vials of an injectable steroid solution from three contaminated lots to healthcare facilities in 23 states. The sterility of this drug product is critical. To relieve chronic pain, it is often injected into patients' spinal columns. After receiving injections of NECC's contaminated steroid, over 50 people have died from complications associated with fungal meningitis and almost 700 others have been stricken with meningitis or other persistent fungal infections. This outbreak ranks as one of the worst public health crises associated with contaminated drugs in the history of the United States, and exposed a fundamental failure in drug safety oversight.

In early October 2012, the Energy and Commerce Committee Majority and Minority staff received briefings from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Massachusetts Department of Public Health (MDPH). On November 14, 2012, the Subcommittee on Oversight and Investigations held a hearing to examine the meningitis outbreak and determine whether it could have been prevented. The Subcommittee subpoenaed the President and co-owner of NECC, Barry Cadden, to appear at the hearing. Mr. Cadden asserted his right against self-incrimination under the Fifth Amendment to the United States Constitution and refused to testify. The Subcommittee also invited FDA Commissioner Margaret Hamburg, M.D., and then-Interim Director of the MDPH Lauren Smith, M.D., MPH, to testify about their agencies' oversight of NECC. Further, the Subcommittee heard testimony from Ms. Joyce Lovelace, the wife of the first known victim. This hearing did not resolve the fundamental question posed: could the meningitis outbreak have been prevented?

Prior to the hearing, the MDPH produced thousands of pages of documents relating to NECC and Ameridose, another Massachusetts company owned and operated by the same family as NECC, which was also involved in large-scale production and distribution of drug products nationwide.<sup>1</sup> The documents detailed the MDPH's history with these firms. FDA, however, produced only a limited number of documents requested by the Committee prior to the November 2012 hearing, consisting of inspection reports and the agency's formal correspondence with NECC and Ameridose. No internal FDA communications were included. NECC has produced some documents, but has largely been unable to respond to the Committee's

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<sup>1</sup> NECC and Ameridose share common ownership and corporate structures. Barry Cadden, his wife, Lisa Conigliaro-Cadden, her brother, Gregory Conigliaro, and his wife, Carla Conigliaro, serve as directors of both companies. NECC is located in Framingham, MA, adjacent to one of the two Ameridose facilities. Ameridose's other facility is located in Westborough, MA.

requests as its files and computers were seized pursuant to a search warrant executed by FDA's Office of Criminal Investigations (OCI) and the Criminal Division of the U.S. Attorney's Office, beginning on October 16, 2012. As a result of this ongoing criminal investigation, the Committee's investigative efforts to date have primarily focused on obtaining and reviewing FDA documents.

Since the hearing, the Committee has pressed FDA to produce all of its documents relating to NECC and Ameridose in order to obtain a full picture of FDA's inspectional history, oversight, and decision-making with respect to these firms. Only after being threatened with the possibility of a subpoena in a February 1, 2013, letter to Commissioner Hamburg, did FDA finally complete its production on March 21, 2013. FDA's production included internal emails between officials and staff at FDA headquarters and staff in FDA District Offices relating to NECC and Ameridose. It also included memoranda and emails exchanged within FDA's Office of the Chief Counsel (OCC) relating to the agency's assessment of its authority over pharmacy compounding. FDA has asserted that all documents and communications responsive to the Committee's requests have been produced.

After reviewing these documents, Majority Committee staff believes there is a strong basis for Members to pursue answers from FDA on whether this tragedy was preventable had the agency taken action under its existing authorities to address the steady stream of complaints it had received about NECC and its sister company, Ameridose, since issuing a Warning Letter to NECC in December 2006. The answer to this question is critical to solving any underlying problems. Operational and/or systemic flaws must be addressed in order to ensure that if any additional laws are passed or administrative actions are taken, they will actually lessen the chances of history repeating itself.

The documents that FDA produced to the Committee are troubling. Contrary to a statement made by Massachusetts Governor Deval Patrick, NECC was not "operat[ing] in the shadows."<sup>2</sup> NECC and Ameridose had long been the topic of significant discussion within FDA; the link between the two companies was well known. Since late 2004, when FDA last inspected NECC prior to the outbreak, the agency received numerous complaints from a range of healthcare providers—and at least one informant at Ameridose—about the companies' products and practices, including many that called into question the safety of the drugs the companies produced.

During the Commissioner's testimony before the Subcommittee in November, and in numerous statements made by her and other FDA officials since, FDA has maintained that uncertainty over its authority prevented the agency from pursuing enforcement actions against companies involved in compounding. For example, in her written statement for the Subcommittee's hearing on November 14, the Commissioner asserted that "FDA's ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and

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<sup>2</sup> Press Release, Mass. Dep't of Health & Human Services, Governor Patrick Announces Legislation to Reform Board of Pharmacy and Fill Gaps in Compounding Industry Oversight (Jan. 4, 2013), *available at* <http://www.mass.gov/eohhs/gov/newsroom/press-releases/eohhs/legislation-to-reform-board-of-pharmacy-announced.html>.

poses risks to patients has been hampered by gaps and ambiguities in the law.”<sup>3</sup> She repeatedly mentioned that FDA’s authority over compounding pharmacies—even when such entities were engaged in activities that closely resembled those of a drug manufacturer—was questionable. The Commissioner stated that the “legal framework for FDA activities is very, very unclear, untested, and limited”<sup>4</sup> and that FDA has “ambiguous, fragmented, unclear, and contested authorities in this particular realm of pharmacy and drug manufacturing practice. . . .”<sup>5</sup> Citing these issues as impediments to FDA’s ability to act in the face of mounting patient safety and public health concerns associated with NECC and Ameridose, the Commissioner proposed a new framework for regulating drug compounding operations and asked Congress for additional “authorities to support this new regulatory paradigm.”<sup>6</sup>

FDA has long been steadfast in its assertions of authority over drug manufacturing being conducted under the guise of pharmacy compounding—and that the agency would enforce such authority when entities like NECC and Ameridose were engaged in significant violations of the Food, Drug, and Cosmetic Act and jeopardizing public health in the process.<sup>7</sup> That being said, internal FDA documents do show that the agency has been grappling with its authority over compounding for decades and that this debate came to a head in early 2009, after two different Circuit Courts of Appeals had issued conflicting opinions on the matter. What is troubling, though, is that FDA allowed this uncertainty to essentially paralyze the agency’s oversight efforts from 2009 through 2012, even with respect to companies operating well outside the bounds of traditional pharmacy compounding, including NECC and Ameridose.

In the six years following the 2006 Warning Letter, FDA failed to take any enforcement action against NECC or Ameridose despite receiving complaint after complaint, often relating to the safety of the companies’ drugs. Though several inspections and related enforcement actions were considered during this time period, they were repeatedly delayed and ultimately cancelled. In fact, in 2011, FDA made an affirmative decision to suspend inspections and enforcement actions relating to compounding operations, including NECC and Ameridose, until the agency finalized new guidance to industry detailing where it would draw the line between pharmacy compounding and drug manufacturing. Regardless of where this line would ultimately have been drawn, based on a review of the documents, it appears evident that NECC and Ameridose had already crossed it.

FDA’s recent decisions not to even re-inspect NECC or Ameridose pursuant to any of the complaints the agency received are perplexing, particularly in light of FDA’s flurry of

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<sup>3</sup> *The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 112th Cong. (2012) (prepared statement of Margaret Hamburg, Comm. of U.S. Food & Drug Admin. (FDA)) [hereinafter, “Hamburg Statement”], available at <http://www.fda.gov/NewsEvents/Testimony/ucm327664.htm>.

<sup>4</sup> *The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 112th Cong. 61-62 (2012) (testimony of Margaret Hamburg, Comm. of FDA) [hereinafter, “Hamburg Testimony”], available at <http://energycommerce.house.gov/hearing/fungal-meningitis-outbreak-could-it-have-been-prevented>.

<sup>5</sup> *Id.* at 74.

<sup>6</sup> *Id.* at 53.

<sup>7</sup> See Jane Axelrad, then-Associate Dir. for Policy, & David Horowitz, then-Dir., Off. of Compliance, Center for Drug Evaluation & Research (CDER), FDA, *FDA Update on Pharmacy Compounding*, Presentation to Int’l Acad. of Compounding Pharmacists (June 9, 2003).

enforcement activity since the meningitis outbreak involving a number of companies engaged in similar practices. According to FDA, since October 1, 2012, the agency has inspected 50 compounding facilities—issuing Form 483s<sup>8</sup> to approximately 30 firms, resulting in five firms recalling their products, and one firm receiving a Warning Letter. FDA staff informed Committee staff that other regulatory actions are under consideration. Like NECC and Ameridose, several of these companies have long histories with FDA. Prior to these inspections taking place, no new laws were passed and no new regulations or guidance documents were issued.

Part II of this memorandum provides a summary of FDA's authority over pharmacy compounding and the agency's related enforcement policies. Parts III and IV will show that, while broader policy discussions about the scope of FDA's authority were ongoing within the agency, a number of FDA employees and officials grew increasingly concerned about the safety of the products and practices at NECC and Ameridose, based on complaints the agency received. Despite its concerns that these companies were jeopardizing patient safety, FDA took no meaningful action against either company since issuing the 2006 Warning Letter to NECC. While the agency has pointed to confusion over its authority, the documents obtained by the Committee reveal that inefficiency, indecisiveness, skewed priorities, and a lack of leadership are what primarily hampered FDA's ability to prevent NECC's products from killing over 50 Americans.

## PART II: FDA AUTHORITY OVER PHARMACY COMPOUNDING

FDA has long defined traditional pharmacy compounding as the combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication for an individual patient.<sup>9</sup> In 1992, due to FDA's concerns that certain compounding pharmacies were producing and distributing unapproved new drugs in a manner that was clearly outside the bounds of traditional pharmacy compounding, the agency issued Compliance Policy Guide 7132.16 (1992 CPG). FDA asserted that compounded drugs were not exempt from the requirements of the Food, Drug, and Cosmetic Act (FDCA or the Act), and while the agency did not intend to initiate enforcement actions against entities involved in traditional pharmacy compounding, it did plan to do so in situations where a company's activities resembled those of a drug manufacturer. A list of non-exhaustive factors the agency would consider in making these determinations was included.

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<sup>8</sup> FDA issues a Form 483 at the end of an inspection when the investigators believe that the observed conditions or practices, in their judgment, may indicate violations of the FDCA or any related regulations. FDA has stated that its goal in issuing a 483 is to have the company act quickly to correct potential violations. The FDA considers the 483 along with an Establishment Inspection Report (EIR), prepared by FDA investigators, and any other information, including any responses received from the company, to determine whether further action is appropriate.

<sup>9</sup> See *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Hearing Before the S. Comm. on Health, Educ., Lab., and Pensions, 108th Cong.* (2003) (prepared statement of Steven Galson, Acting Dir., CDER, FDA), available at <http://www.fda.gov/NewsEvents/Testimony/ucm115010.htm>.

In 1997, based on concerns from compounding pharmacists that, according to the 1992 CPG, they were operating in *per se* violation of the FDCA, Congress added section 503A to the Act as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA). Congress's intent in doing so was to "bring the legal status of compounding in line with FDA's longstanding enforcement policy of regulating only drug manufacturing, not ordinary pharmacy compounding."<sup>10</sup> Section 503A exempts compounded drugs from the new drug requirements and certain adulteration and misbranding provisions of the FDCA so long as certain conditions are met. The conditions listed in the statute parallel the factors included in the 1992 CPG and are intended to limit the exemptions from the FDCA's requirements to traditional pharmacy compounding. These conditions include that the compounding be performed by a licensed pharmacist or physician, that it is done in response to a patient-specific prescription, and that the compounded product is necessary for an identified patient. Section 503A also required that the physician's prescription must be unsolicited and the pharmacy must not advertise or promote the compounding of any particular drug.<sup>11</sup>

The provisions related to solicitation and advertising were challenged in court by a group of pharmacists as impermissible regulation of commercial speech. In February 2001, the U.S. Court of Appeals for the Ninth Circuit agreed and declared that the speech-related provisions were non-severable from the remainder of section 503A and, therefore, the entire section was invalid.<sup>12</sup> In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the U.S. Supreme Court affirmed the Ninth Circuit's decision with respect to the First Amendment restrictions, but did not rule on the issue of severability.

Because of the uncertainty caused by the Supreme Court's decision in *Western States*, FDA re-issued an updated version of its 1992 CPG in May 2002. Compliance Policy Guide, Section 460.200 (2002 CPG) was very similar to the 1992 CPG; it reaffirmed FDA's authority over compounding under the FDCA and listed nine non-exhaustive "factors the Agency will consider in exercising its enforcement discretion regarding pharmacy compounding," including compounding copies of drugs that are commercially available and compounding drugs for third parties who resell to individual patients.<sup>13</sup> According to the document: "FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act. Such establishments and their activities are the focus of this guidance. . . . Pharmacies engaged in activities analogous to manufacturing and distributing drugs for human use may be held to the same provisions of the Act as manufacturers."<sup>14</sup>

In early 2005, another group of pharmacies brought suit—this time in Texas—contesting FDA's authority to regulate compounded drugs under the FDCA. On appeal, the case reached the Fifth Circuit. In *Medical Center Pharmacy v. Mukasey*, 536 F. 3d 383 (5th Cir. 2008), the

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<sup>10</sup> 143 Cong. Rec. S9839 (daily ed. Sept. 24, 1997) (statement of Sen. Kennedy).

<sup>11</sup> See 21 U.S.C. § 353.

<sup>12</sup> *Western States Medical Center v. Shalala*, 238 F. 3rd 1090 (9th Cir. 2001).

<sup>13</sup> See Compliance Policy Guide, Sec. 460.200 Pharmacy Compounding, FDA (May 2002) [hereinafter, "2002 CPG"], available at <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm>

<sup>14</sup> *Id.* at 3.

U.S. Court of Appeals for the Fifth Circuit refused to be bound by the Ninth Circuit's decision in *Western States*, and held in July 2008 that the unconstitutional restrictions on commercial speech were in fact severable from the rest of section 503A, which should remain in effect. Therefore, in the Fifth Circuit, compounded drugs are exempt from the new drug, manufacturing, labeling, and other requirements of the FDCA, but only to the extent that the pharmacy complies with the restrictions set out in section 503A. Until the *Medical Center Pharmacy* decision, FDA had been operating under the assumption that section 503A was invalid in its entirety; therefore, as the agency stated in litigation and various correspondence over the previous six years, compounded drugs were subject to the FDCA requirements but FDA would continue to exercise enforcement discretion nationwide, as articulated in the 2002 CPG. After the decision, FDA publicly took the position that it would apply the non-commercial speech related provisions of section 503A in the Fifth Circuit and continue to exercise enforcement discretion with respect to entities located outside the Fifth Circuit. Within FDA, however, debate about the soundness of this approach would continue. These discussions and how they impacted potential enforcement actions against NECC and Ameridose will be addressed throughout this memorandum.

Publicly, FDA has consistently asserted authority over compounding pharmacies engaged in activities more analogous to those of a drug manufacturer. In fact, on June 29, 2012—only days after NECC made and distributed two contaminated batches of methylprednisolone acetate to facilities across the country—FDA released a statement to that effect: “FDA may take enforcement action against compounding pharmacies if warranted. The FDA makes its enforcement decisions about compounded products on a case-by-case basis after considering the particular facts at issue.”<sup>15</sup> In a related letter sent to one large-scale compounding pharmacy on the same day, FDA stated that the agency is “applying its normal enforcement policies for compounded drugs” and that the compounding of large volumes of drugs that are essentially copies of FDA-approved products is one factor “the Agency considers in deciding whether to initiate enforcement action with respect to compounding.”<sup>16</sup> The letter highlighted that these factors are addressed “in both section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. § 353a) and the Agency’s compliance policy guide (CPG) on pharmacy compounding (CPG Sec. 460.200).”<sup>17</sup> The letter then included a footnote discussing the fact that “the Fifth and Ninth Circuit Courts of Appeals have reached different conclusions regarding whether section 503A is invalid or remains in effect.”<sup>18</sup>

In her written statement for the November 14, 2012, Oversight Subcommittee hearing, Commissioner Hamburg cited this Circuit Court split as having “amplified the perceived gaps and ambiguity associated with FDA’s authority over compounding pharmacies.”<sup>19</sup> While there were challenges to FDA’s authority, at no point in time did the agency lack sufficient authority

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<sup>15</sup> Press Announcement, FDA, Questions and Answers on Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate (the active ingredient in Makena) (June 29, 2012), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310215.htm>.

<sup>16</sup> Letter from Dir. (acting), Off. of Unapproved Drugs and Labeling Compliance, Off. of Compliance, CDER, FDA, to Pres. & CEO, Wedgewood Pharmacy (June 29, 2012), available at <http://www.fda.gov/downloads/NewsEvents/Newsroom/PressAnnouncements/UCM314387.pdf>.

<sup>17</sup> *Id.* at 2.

<sup>18</sup> *Id.*

<sup>19</sup> Hamburg Statement, *supra* note 3.

under the FDCA to take enforcement action against companies that were clearly manufacturing under the guise of compounding and jeopardizing patient safety in the process. Regardless of whether FDA applied and cited to the factors listed in section 503A or the CPG, NECC and Ameridose were operating well outside the scope of traditional compounding pharmacies and squarely within FDA's authority to take action in response to violations of the FDCA.

### PART III: FDA'S OVERSIGHT OF NECC: 2003-2006

NECC first appeared on FDA's radar in March 2002, when two adverse events were reported to the agency through its MedWatch system. Both adverse events involved patients experiencing meningitis-like symptoms after receiving betamethasone injections from the same lot produced and distributed by NECC. Based on the ensuing inspection, which was conducted with the MDPH, FDA issued NECC a Form 483 on April 16, 2002. FDA focused primarily on two violations: the sterility of the betamethasone product and NECC's failure to account for records related to the suspect lot of betamethasone, which subsequently tested positive for contamination.<sup>20</sup>

In October 2002, FDA and State inspectors returned to NECC in response to three MedWatch reports associated with the use of methylprednisolone acetate made by NECC in May 2002. Like betamethasone, methylprednisolone acetate is a steroid solution often injected into the spine to treat pain and swelling. According to FDA's investigative report, the three MedWatch reports involved patients having to be hospitalized with meningitis-like symptoms. Hospital staff informed FDA that vials from the same lot distributed by NECC were tested at the hospital and confirmed positive for contamination.<sup>21</sup> In February 2003, prior to FDA's issuance of another Form 483 to NECC, a meeting was convened with officials from FDA and the MDPH, at which time it was decided that NECC should be treated as a compounding pharmacy and that the State should take the lead on any further regulatory actions.<sup>22</sup>

Part III(A) of this memorandum will show that, not long after the February meeting, FDA began to receive additional information about the nature and scope of NECC's operations that would raise questions about whether the company was in fact operating as a manufacturer, as opposed to a traditional compounding pharmacy. This information would form the basis for an additional inspection beginning in September 2004. As described in Part III(B), FDA's extraordinary delay in issuing a Warning Letter to NECC pursuant to that inspection interfered with FDA's efforts to address new complaints that were submitted between the time of the 2004 inspection and a Warning Letter ultimately being issued in December 2006. Moreover, FDA's failure to address NECC's January 2007 response to the Warning Letter until almost another two years had passed further complicated FDA's enforcement efforts. Part III(C) details the

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<sup>20</sup> See FDA, NEW ENGLAND COMPOUNDING PHARMACY, INC. FORM FDA 483 (Apr. 16, 2002).

<sup>21</sup> FDA, INSPECTION REPORT OF NEW ENGLAND COMPOUNDING CENTER, at 4 (Feb. 10, 2003) [hereinafter, "FDA FEB. 10, 2003 INSPECTION REPORT"].

<sup>22</sup> See Memorandum from Kristina Joyce, Consumer Safety Officer, New England Dist. Off., FDA & Mark Lookabaugh, Compliance Officer, New England Dist. Off., FDA, to Central File, *February 5, 2003 Meeting with Massachusetts Board of Pharmacy/Division of Professional Licensure (239 Causeway Street, Boston, MA 02114)*, at 1 (Feb. 24, 2003) [hereinafter, "Feb. 24, 2003, FDA Memorandum"].

complaints that FDA continued to receive about NECC after the agency replied, on October 31, 2008, to NECC’s response to the Warning Letter. Despite considering several additional inspections of NECC, FDA did not return to the company until the fungal meningitis outbreak.

*A. FDA is on Notice that NECC is Operating Outside the Scope of a Traditional Compounding Pharmacy.*

FDA has long recognized the importance of traditional pharmacy compounding and acknowledged that the State is primarily responsible for overseeing pharmacies engaged in this often critical practice. However, according to FDA’s policy guidance, “when the scope and nature of a pharmacy’s activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the [FDCA], FDA has determined that it should seriously consider enforcement action.”<sup>23</sup> Documents produced to the Committee show that prior to FDA’s issuance of the Warning Letter to NECC the agency understood that the company was substantially engaged in activities resembling those of a drug manufacturer.

As was previously mentioned and discussed at the November 2012 hearing with Commissioner Hamburg, a meeting was convened in February 2003 between FDA and the MDPH, which included representatives from the Massachusetts Board of Registration in Pharmacy (MBP or Massachusetts Board). The purpose of the meeting was to “review the inspectional history of the New England Compounding Center and develop a joint strategy for achieving safe compounding practices at the firm.”<sup>24</sup> At this point in time, FDA and State inspectors had already been to NECC on two separate occasions—in April and October 2002—in response to MedWatch reports associated with patients experiencing meningitis-like symptoms after having been administered NECC-produced betamethasone and methylprednisolone acetate injections.

During the February 2003 meeting, “[a] discussion was held to decide if NECC should be considered a manufacturer or a compounder.”<sup>25</sup> It was decided that “current findings supported a compounding role” and that “the state would be in a better position to gain compliance or take regulatory action against NECC as necessary.”<sup>26</sup> While FDA determined that the Massachusetts Board would take the lead, FDA concluded the meeting by “emphasizing the potential for serious public health consequences if NECC’s compounding practices, in particular those relating to sterile products, are not improved.”<sup>27</sup> Prior to this meeting taking place, David Elder, FDA’s then-Director of Compliance in the New England District Office (NWE-DO) had emailed individuals in the Division of New Drugs and Labeling Compliance (DNDLC) at FDA’s Center for Drug Evaluation and Research (CDER), acknowledging the need for FDA to continue to monitor the situation at NECC and the State’s oversight of the firm. He stated, “We will have further discussions with the state about any future actions with this company – if the state can’t

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<sup>23</sup> 2002 CPG, *supra* note 13, at 3.

<sup>24</sup> Feb. 24, 2003, FDA Memorandum, *supra* note 22.

<sup>25</sup> *Id.* at 2.

<sup>26</sup> *Id.*

<sup>27</sup> *Id.*

or won't take appropriate action, we will work with your office to devise an appropriate enforcement strategy as we remain concerned with this firm's operations.”<sup>28</sup>

When asked about FDA's role at the hearing in November 2012, Commissioner Hamburg stated, “[FDA] tried to provide help and assistance. But the responsibility for assuring compliance with sterility issues was, in fact not our direct responsibility.”<sup>29</sup> When questioned about whether she thought the State “could have stopped [the meningitis outbreak],” Commissioner Hamburg responded, “They were unsuccessful, and it is, you know, was tragic.”<sup>30</sup> What Commissioner Hamburg failed to mention was that the snapshot FDA had of the company in February 2003 was very different from the deep understanding the agency had gained about the nature and scope of NECC's operations from 2003 up until the outbreak in 2012.

In fact, not long after the February 2003 meeting, a different picture of NECC began to emerge. On May 26, 2004, the Massachusetts Board received an email from a hospital pharmacist in Iowa suggesting that NECC was engaged in manufacturing, not traditional compounding. The pharmacist informed the MBP that “I have been receiving a lot of literature from [NECC] promoting compounded products for cataract surgery. . . . I was told I could easily get 15 patients out of every 3ml dropper of solution, so it would be very economical.”<sup>31</sup> The pharmacist then stated, “Though I strongly believe in the right of pharmacists to compound prescriptions for their patients, the distribution of products under these circumstances looks much more like manufacturing than dispensing.”<sup>32</sup> Based on other documents produced to the Committee, it appears as though the product being referenced was known as trypan blue, reportedly being used for capsular staining during cataract surgery. The lead attorney for the MBP, Susan Manning, asked the Board's Executive Director, Charles Young, in response, “Could you clarify what we may not have known about their operation previously that this email tells us? As in what the FDA might not know in their prior assessment that NECC was not a ‘manufacturer’?”<sup>33</sup>

The MBP forwarded this correspondence to FDA along with a copy of a complaint it had received from a pharmacist in Wisconsin about NECC promoting a potent topical anesthetic cream.<sup>34</sup> At this point in time, FDA had in fact already received a complaint from a law firm representing a drug company related to NECC's promotion of trypan blue. On February 27, 2004, the firm informed FDA that its client had a similar, FDA-approved ophthalmic dye and that, while trypan blue had been approved in certain countries, it was not approved in the U.S.<sup>35</sup> Like the complaints that were forwarded to FDA by the MBP, this complaint raised further

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<sup>28</sup> E-mail from David Elder, Dir. of Compliance, New England Dist. Off., FDA, to Fred Richman, Dep. Dir., Div. of New Drugs & Labeling Compliance (DNDLC), Off. of Compliance, CDER, FDA, et al. (Jan. 23, 2003, 10:48 AM).

<sup>29</sup> Hamburg Testimony, *supra* note 4, at 63-64.

<sup>30</sup> *Id.* at 137.

<sup>31</sup> E-mail from Redaction to Mass. Bd. of Registration in Pharmacy (May 26, 2004, 6:16 PM).

<sup>32</sup> *Id.*

<sup>33</sup> E-mail from Susan Manning, Counsel to Mass. Bd. of Registration in Pharmacy, to Charles Young, Exec. Dir., Mass. Bd. of Registration in Pharmacy (May 27, 2004, 9:49 AM).

<sup>34</sup> See E-mail from Compliance Officer, New England Dist. Off., FDA, to Kathleen Anderson, Acting Team Leader, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA (June 23, 2004, 12:42 PM).

<sup>35</sup> See E-mail from Compliance Officer, New England Dist. Off., FDA, to Kathleen Anderson (Feb. 27, 2004, 10:49 AM).

questions about whether NECC was operating as a traditional compounding pharmacy or as a drug manufacturer. It was apparently the complaints related to trypan blue that prompted CDER to send the NWE-DO an inspection assignment for NECC on June 2, 2004, “to obtain information about the firm’s compounding practices, especially as they relate to the compounding of trypan blue products.”<sup>36</sup> Included in the inspection assignment was an acknowledgement that section 503A of the FDCA had been invalidated by the *Western States* decision so the inspection was being conducted in accordance with the 2002 CPG. It listed a number of questions that “are consistent with that guidance” for the inspector to answer based on information obtained from NECC.<sup>37</sup> The Ninth Circuit’s invalidation of section 503A, therefore, did not preclude FDA from inspecting NECC and, as described in the 2002 CPG, from considering enforcement actions if “the scope and nature of [the] pharmacy’s activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act.”<sup>38</sup>

Pursuant to FDA’s observations during this inspection, which began in September 2004 and was again conducted with State inspectors, NECC was issued a Warning Letter more than two years later, on December 4, 2006. The Warning Letter listed a number of practices that FDA inspectors observed during the inspection of NECC, or which were otherwise brought to the agency’s attention, that indicated the company was operating as a manufacturer. In particular, the Warning Letter stated that the firm was compounding copies of commercially available products, pointing to the fact that trypan blue had since been approved by the FDA in December 2004; compounding standardized anesthetic drug products, which was outside the scope of traditional pharmacy compounding; repackaging Avastin, a sterile injectable product being used to treat macular degeneration; and reportedly informing physicians’ offices that using a staff member’s name on prescriptions would suffice, rather than submitting prescriptions to be filled based on the needs of an identified patient.<sup>39</sup> FDA concluded the Warning Letter by informing the President and co-owner of NECC, Barry Cadden, that “[f]ailure to promptly correct these deviations may result in additional regulatory action without further notice, including seizure or injunction against you and your firm.”<sup>40</sup>

In December 2006, FDA warned Mr. Cadden that a subsequent inspection would be conducted. FDA failed to do so. When asked about this, Commissioner Hamburg testified in November: “We have also been reviewing actions taken in the past with regard to NECC. From our view thus far, we have no reason to believe that any of the specific actions in question, a more timely issuance of the 2006 Warning Letter, or inspectional follow-up, would have prevented this tragedy.”<sup>41</sup> She elaborated, “It is very hard to know if any one action that we might have taken could have stopped this terrible tragedy. I wish that I could identify what that would be.”<sup>42</sup>

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<sup>36</sup> Inspection Request from Kathleen Anderson to Dir., Investigations Branch, New England Dist. Off., FDA (June 2, 2004).

<sup>37</sup> *Id.*

<sup>38</sup> 2002 CPG, *supra* note 13, at 3.

<sup>39</sup> Warning Letter (NEW-06-07W) from Gail T. Costello, Dist. Dir., New England Dist. Office, FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (Dec. 4, 2006) [hereinafter, “FDA Warning Letter”].

<sup>40</sup> *Id.* at 5.

<sup>41</sup> Hamburg Statement, *supra* note 3.

<sup>42</sup> Hamburg Testimony, *supra* note 4, at 138.

What Commissioner Hamburg did not discuss was the fact that complaints about NECC continued well after the Warning Letter; that they were often associated with issues different in nature and scope than those addressed in the Warning Letter; that they were at times related to the safety and potency of NECC products; that FDA failed to inform the State about the complaints; and that FDA considered—but never conducted—several additional inspections of NECC and related enforcement actions that very well may have averted this tragedy. Parts II(B) and (C) detail these complaints and contemplated actions.

*B. After Issuing the 2006 Warning Letter to NECC, FDA Receives More Complaints About NECC Products and Practices*

Following FDA's September 2004 inspection of NECC to investigate the trypan blue complaints, FDA continued to receive new complaints about the company's products and practices. On January 14, 2006, Steven Silverman, then-Director of CDER's Division of New Drugs and Labeling Compliance (DNDLC), was forwarded an email from an individual in Texas detailing NECC's distribution of multiple-use vials of injectable methotrexate, a drug being used to treat certain types of arthritis and rheumatic conditions. The email stated, "In order to process an order they only need the physician's name and telephone number. . . . They do not need or desire to have the patient[']s name."<sup>43</sup> On a subsequent but related exchange, he attached Samia Nasr, then-Team Leader of CDER's Compounding Team, and stated, "As we discussed, NECC is a repeat player, so it might deserve attention that other operations wouldn't merit. But the team is caught up with a range of high-profile issues, so this may need to wait (especially absent reported injury)."<sup>44</sup> No substantive reply to this email was produced to the Committee, though on February 24, 2006, Ms. Nasr was forwarded another NECC solicitation from a consumer safety officer in CDER. This time, in addition to highlighting the firm's Avastin repackaging services, NECC was offering several compounded sterile injectable products.<sup>45</sup>

In forwarding the solicitation, the consumer safety officer stated, "The scope of their manufacturing seems to be beyond the limited concern we have already identified with the Avastin manipulation!" and "in light of the new information suggesting that the scope of drug manufacturing operations at this firm are expanding, the issuance of the directed inspection request is appropriate."<sup>46</sup> Ms. Nasr responded, "I do not have any problem with the inspection, we will know what is going on. I think what we were thinking is that if we send a [Warning Letter] now . . . [FDA] will not be able to send a second one. I do not think OCC [Office of the Chief Counsel or Chief Counsel's Office] will allow us to do that, correct?"<sup>47</sup>

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<sup>43</sup> E-mail from Redaction to Steven Silverman, Dir., DNDLC, Off. of Compliance, CDER, FDA, et al. (Jan. 14, 2006, 6:49 PM).

<sup>44</sup> E-mail from Steven Silverman to Dep. Dir., Div. of Manufacturing & Product Quality, Off. of Compliance, CDER, FDA, et al. (Jan 17, 2006, 11:20 AM).

<sup>45</sup> See E-mail from Supervisory Consumer Safety Officer, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr, Team Leader, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, et al. (Feb. 24, 2006, 1:08 PM).

<sup>46</sup> *Id.*, and E-mail from Supervisory Consumer Safety Officer to Samia Nasr et al. (Mar. 1, 2006, 9:30 AM).

<sup>47</sup> E-mail from Samia Nasr to Supervisory Consumer Safety Officer, et al. (Mar. 2, 2006, 6:05 AM).

The Warning Letter was ultimately sent in December 2006. NECC responded one month later, noting that “the Warning Letter is based on an inspection of NECC that started on September 23, 2004, approximately twenty-eight months ago” and that “[s]ome of the letter’s assertions no longer apply to NECC’s operations.”<sup>48</sup> After disputing FDA’s authority over compounded drugs, Mr. Cadden stated that “NECC does not compound copies of FDA-approved commercially available drugs, introduce unapproved new drugs into interstate commerce, does not need approved [New Drug Applications] before dispensing its compounded medications, and does not process or repackage approved drugs in a manner that would subject us to FDA regulation. Nor are our compounded medications misbranded. NECC dispenses compounded medications upon the receipt of valid prescriptions.”<sup>49</sup>

After reviewing NECC’s letter, Mr. Silverman emailed several colleagues in CDER on January 9, 2007, including Ms. Nasr and CDER’s Director of Compliance at the time, Deborah Autor. He stated, “In my view, NECC’s response is unacceptable. . . . If you disagree, let’s discuss. Otherwise, we need a response to this letter. And given the comments about the timeliness of the Warning Letter (OCC’s fault), we need a response within a reasonable time frame.”<sup>50</sup>

FDA’s response letter was not ultimately sent until October 31, 2008. Soon after the Warning Letter was issued in 2006, however, new complaints about NECC had already begun to arrive. It is apparent from documents produced to the Committee that FDA considered additional inspections and potential enforcement activities throughout this time period, but FDA’s failure to issue a timely response to NECC’s January 2007 reply letter thwarted any agency action.

Soon after FDA received NECC’s response, on February 22, 2007, a compliance officer in the NWE-DO received an envelope of documents from an anonymous sender. The compliance officer forwarded copies of the documents to several of her colleagues in the District Office stating, “It appears from the words she highlighted on the documents, that she wants me to know about other violations of NECC [than those described in the Warning Letter]. . . . I will send the information to CDER. Note that all the documents she sent me pre-date the [Warning Letter]; however, this information can be used for the [Warning Letter] follow-up inspection assignment.”<sup>51</sup> Similar to the NECC solicitation FDA had been forwarded a year earlier, in addition to the Avastin repackaging services being offered, the documents included advertisements for a number of compounded sterile injectable products.

While these complaints did not involve patients being harmed by NECC products, they did provide FDA with additional knowledge about the nature and scope of the company’s operations. On June 25, 2007, however, FDA did receive an adverse event report directly implicating Avastin that had been repackaged by NECC and administered to a patient to treat

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<sup>48</sup> Letter from Barry J. Cadden, Dir. of Pharmacy, NECC, to Compliance Officer, New England Dist. Off., FDA, et al., at 1 (Jan. 5, 2007).

<sup>49</sup> *Id.* at 3.

<sup>50</sup> E-mail from Steven Silverman to Deborah Autor, Dir., Off. of Compliance, CDER, FDA, et al. (Jan. 9, 2007, 3:20 PM).

<sup>51</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi, Dir., Compliance Branch, New England Dist. Off., FDA, et al. (Feb 22, 2007, 11:30 AM).

macular degeneration. According to the report, the patient had received six monthly doses of Avastin without incident until April 21, 2007, when “the patient developed severe endophthalmitis” and had to undergo emergency eye surgery.<sup>52</sup> The report stated, “The Avastin dose administered prior to event onset was provided to the [reporting physician] by the New England Compounding Center.”<sup>53</sup> No communications referring or relating to this complaint were produced to the Committee by FDA. It is not apparent, based on a review of the documents, that FDA did anything in response—let alone re-inspect NECC—despite primarily detailing these very concerns in the Warning Letter: “We are especially concerned with the potential microbial contamination associated with splitting Avastin – a single-use, preservative-free, vial – into multiple doses. When used intravitreally, microbes could cause endophthalmitis, which has a high probability for significant vision loss.”<sup>54</sup>

The decision over whether FDA would re-inspect NECC pursuant to the new complaints was clearly being influenced by the agency’s inability to send a timely response to NECC’s January 2007 letter replying to the Warning Letter. Further, the outstanding response was also influencing FDA’s decision whether to inspect Ameridose, NECC’s sister company. On May 21, 2007, CDER drafted an inspection request for the NWE-DO based on a MedWatch report FDA received associated with Ameridose, which made similar complaints to those FDA had already received about NECC. The complaint stated that “Ameridose is engaged in the manufacture of unapproved intravenous solutions that are not dispensed pursuant to a prescription. . . .”<sup>55</sup> When one of the inspectors in the District Office received the request from CDER, he emailed his supervisor asking, “Do we want to inspect with the state this new location under the same or similar management/ownership prior to responding to the NECC response of January 7, 2007?”<sup>56</sup> The supervisor responded that CDER was “aware of the relationship between NECC and Ameridose” but that they “still want[ ] you to go to Ameridose” after calling them to discuss the approach.<sup>57</sup> However, the Ameridose inspection did not ultimately occur until December 2007. Prior to the inspection, the District Office inspector contacted an individual on CDER’s Compounding Team who asked him to obtain information during the inspection to “elaborate on their business relationship/model and anything else that may potentially cause some inspectional hurdles.”<sup>58</sup> This inspection and decisions surrounding it, as well as additional issues with Ameridose and the relationship between the two entities, are subsequently addressed in greater detail in Part IV of this memorandum.

Meanwhile, new complaints directly associated with the safety of NECC products continued. On December 6, 2007, FDA’s Office of Emergency Operations received a call from a

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<sup>52</sup> FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (June 25, 2007).

<sup>53</sup> *Id.*

<sup>54</sup> FDA Warning Letter, *supra* note 39, at 3.

<sup>55</sup> Inspection Request from Staff Fellow, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk, Dir., Investigations Branch, New England Dist. Off., FDA, (May 21, 2007).

<sup>56</sup> E-mail from Drug Pre-Approval Manager, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (June 7, 2007, 9:05 AM).

<sup>57</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Drug Pre-Approval Manager, New England Dist. Off., FDA (June 7, 2007, 11:49 AM).

<sup>58</sup> E-mail from Reg. Operations Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Drug Pre-Approval Manager, New England Dist. Off., FDA (Dec. 4, 2007, 10:55 AM).

“physician pain specialist who treats patients with epidural injections.”<sup>59</sup> The caller stated that “[f]or a period of time, he was treating fibromyalgia patients with epidural injections of betamethasone manufactured by New England Compounding Center” and that “between August 22 and October 5 he noticed that some vials of product were discolored (which he discarded) but others, which appeared normal, were administered and his patients started having problems.”<sup>60</sup>

Based on a memorandum drafted by a consumer safety officer in FDA’s New Orleans District Office (NOL-DO) assigned to investigate the complaint, she first visited the physician’s office on December 11, 2007.<sup>61</sup> The memorandum detailed a series of meetings and interviews conducted with the physician and several patients through January 2008, which raised numerous concerns about the activities of the physician and his practices. While the physician failed to produce certain records, dates, and patient information requested, he did state that “greater than 100 patients that were treated with the betamethasone began complaining of increased fibromyalgia pain and moderate to severe flu-like symptoms”; that he noticed “some of the vials of betamethasone appeared to be discolored”; and that “particles [were] floating in the bottom of the vial.”<sup>62</sup> He also said that “the lots in question were received on 8/20/07, 9/17/07, and 9/28/07”<sup>63</sup> and provided the FDA investigator with “vials of the questionable betamethasone”<sup>64</sup> he had not discarded from one of these lots, which she retained for sampling. She ultimately referred the complaint to the NWE-DO “for follow-up as appropriate” on February 25.<sup>65</sup>

It is apparent from subsequent District Office communications produced to the Committee that FDA tested the vials provided by the physician, but those tests did not detect the presence of any bacterial endotoxins and the samples met “FDA requirements for assay and ID.”<sup>66</sup> After reviewing the memorandum and the test results, the NWE-DO compliance officer forwarded the information to Ms. Nasr in CDER on April 1, 2008, and followed up on May 22 asking, “Any decision on any type of follow-up?”<sup>67</sup> No response from Ms. Nasr was produced to the Committee, though this conversation between the District Office and CDER continued for some time.<sup>68</sup> FDA did not re-inspect NECC pursuant to this complaint. Further, based on documents produced to the Committee, it does not appear as though FDA contacted the company or informed the State about these new concerns with NECC’s betamethasone injections.

FDA’s decision not to re-inspect NECC based on this complaint is troubling, given that the initial inspection of NECC in 2002 was triggered by adverse event reports associated with patients experiencing similar symptoms after receiving the same drug. FDA’s delay in resolving the 2006 Warning Letter appears to have influenced the agency’s response. For example, on

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<sup>59</sup> E-mail from Emergency Coordinator, Off. of Crisis Mgmt., Off. of Emergency Operations, FDA, to Supervisor, New Orleans Dist. Off., FDA (Dec. 6, 2007, 1:53 PM).

<sup>60</sup> *Id.*

<sup>61</sup> See Memorandum from Consumer Safety Officer, New Orleans Dist. Off., FDA, to Supervisory Consumer Safety Officer, New Orleans Dist. Off., FDA (January 9, 2008) (note that Memorandum is accidentally dated 2007).

<sup>62</sup> *Id.* at 2.

<sup>63</sup> *Id.*

<sup>64</sup> *Id.* at 3.

<sup>65</sup> *Id.* at 1.

<sup>66</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr (Apr. 1, 2008, 2:44 PM).

<sup>67</sup> May 22, 2008 email from Ota to Nasr.

<sup>68</sup> See May 29, 2008 email from Ota to Anderson.

June 17, 2008, FDA received separate, though related, information about betamethasone being made and distributed by NECC. Representatives of a pharmaceutical distributor met with NOL-DO staff to express concerns about compounded betamethasone “being injected in the spinal synovial fluid.”<sup>69</sup> Three different sizes of NECC vials were shared with NOL-DO staff who forwarded the information to the NWE-DO.<sup>70</sup> Once the NWE-DO compliance officer responsible for NECC received it on June 24, he forwarded it to Ms. Nasr in CDER stating, “The District usually follows up with these memos by inspecting the firms listed in the memo but the NECC [Warning Letter case] is still open and we do not usually re-inspect until an adequate response is received from the firm. I know the last time we spoke you expressed that you might want to issue an assignment to inspect NECC. Please advise on follow-up to the memo?”<sup>71</sup> Ms. Nasr responded, “We received information also about NECC compounding mesotherapy products<sup>72</sup> and we were thinking about inspection. Can we set up a call with you and others to discuss?”<sup>73</sup>

Ms. Nasr informed Mr. Silverman, who at this point had been promoted to Assistant Director of CDER’s Office of Compliance, and Kathleen Anderson, Deputy Director of the DNDLC, that she had spoken with NWE-DO staff about the inspection and the question came up about what they would do “if they find violations and we end up needing to issue another warning letter.”<sup>74</sup> Ms. Anderson replied, “Typically we do not issue a firm a warning letter for the same violation (unless it has been many years since the initial warning letter). Sometimes we issued more than one warning letter to a firm if the letters are to address different unrelated issues. If we have issued multiple letters, for the same or similar problems then we should be considering seizure or injunction rather than another warning letter.”<sup>75</sup>

CDER decided to go forward with the inspection of NECC and began drafting an assignment for the District Office. On June 27, 2008, Ms. Nasr spoke with the compliance officer in the NWE-DO responsible for NECC. The compliance officer informed Mutahar Shamsi, then-Director of Compliance in the District Office, “Today Samia [Nasr] called me and she said she talked with people in [CDER] and they said if the firm is still compounding then we will enjoin the firm.”<sup>76</sup> The assignment was ultimately issued on September 16, 2008, and stated, “The purpose of this inspection request is to investigate the site’s compounding practices, particularly relating to the production of mesotherapy/lipodissolve products.”<sup>77</sup> It is clear from the assignment that in addition to the mesotherapy-specific issues, the inspector was to follow-up on the observations documented in the December 2006 Warning Letter and to investigate the firm’s compounding operations in general. In particular, as indicated by a list of questions for

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<sup>69</sup> Memorandum from Compliance Officer, New Orleans Dist. Off., FDA, to File (June 17, 2008).

<sup>70</sup> *See id.*

<sup>71</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr (June 24, 2008, 11:38 AM).

<sup>72</sup> Mesotherapy products have been advertised as an alternative to liposuction. They have been compounded with phosphatidylcholine. Although phosphatidylcholine is approved by the FDA as a dietary supplement, compounders have prepared the product for injection.

<sup>73</sup> E-mail from Samia Nasr to Compliance Officer (June 24, 2008, 11:42 AM).

<sup>74</sup> E-mail from Samia Nasr to Kathleen Anderson, et al. (June 25, 2008, 6:43 AM).

<sup>75</sup> E-mail from Kathleen Anderson to Samia Nasr (June 25, 2008, 8:48 AM).

<sup>76</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi (June 27, 2008, 1:15 PM).

<sup>77</sup> Inspection Request, Sample Collection from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk & Gail Costello, at 1 (Sept. 16, 2008).

the inspector to address, sterility was a concern: “Are drug products and supplies stored under appropriate temperature, light, moisture, sanitation, and ventilation conditions?”; “Are sterile products made in an environment that prevents contamination?”; and “What type of in-process or finished product testing [is] performed and at what frequency?” The assignment concluded, “Based on the determination if the firm is operating as [a] manufacturer or as [a] traditional compounding pharmacy, an enforcement action is likely if the firm is operating as [a] manufacturer.”<sup>78</sup>

Once Mr. Shamsi received the assignment on September 18, 2008, he forwarded it to Deborah Autor in CDER asking, “Did you want to get involved also at the beginning? Since the firm has already received a Warning Letter, further violations should (I hope) lead to a judicial action.”<sup>79</sup> After hearing from several of her colleagues in CDER, Ms. Autor replied on September 25, “I’m told the [CDER] compounding team is now talking to and collaborating with the District on this hybrid mesotherapy/general compounding inspection. Let me see if the GMP side of my office also wants to engage now to prepare for that part of the inspection.”<sup>80</sup> She proceeded to reach out to then-Director of CDER’s Division of Manufacturing and Product Quality, Rick Friedman, asking for his thoughts, to which he replied, “[W]e could assist with manufacturing and sterility assurance issues in a pre-inspection briefing[.]”<sup>81</sup>

While CDER appeared ready to go forward with the inspection—despite the fact that the agency had yet to send NECC a response to its January 2007 letter objecting to the findings in the Warning Letter—it is apparent that Mr. Shamsi began to question whether it was wise to inspect the facility prior to issuing the response. On October 1, 2008, he emailed Ms. Autor stating, “I’m wondering whether our lack of a response would hinder any further regulatory action against NECC (if OGC is reluctant to respond to a [Warning Letter], how would they respond to an injunction request?)[.]”<sup>82</sup> To a certain extent, Mr. Shamsi’s concerns were shared by the NECC compliance officer in the NWE-DO: “If we re-inspect there is no second [Warning Letter.] Next step is to enjoin the firm. . . . Injunctions have time frames and have to be processed quickly. If OCC and CDER cannot agree on a response letter can they agree on an injunction[?]”<sup>83</sup>

By this point, documents produced to the Committee reveal that FDA staff was frustrated with the time it was taking the FDA Chief Counsel’s Office to approve a response to NECC. In fact, in January 2008, Mr. Silverman had asked whether anyone in CDER was having any particularly frustrating interactions with OCC they would like addressed.<sup>84</sup> On January 28, Ms. Nasr responded that the Compounding Team was concerned about the “length of time to get

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<sup>78</sup> *Id.* at 6.

<sup>79</sup> E-mail from Mutahar Shamsi to Deborah Autor (Sept. 18, 2008, 1:44 PM).

<sup>80</sup> E-mail from Deborah Autor to Mutahar Shamsi (Sept. 25, 2008, 11:29 PM).

<sup>81</sup> E-mail from Rick Friedman, Dir., Div. of Manufacturing & Product Quality, Off. of Compliance, CDER, FDA, to Deborah Autor (Sept. 26, 2008, 12:31 AM).

<sup>82</sup> E-mail from Mutahar Shamsi to Deborah Autor (Oct. 1, 2008, 8:19 AM).

<sup>83</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi (Oct. 2, 2008, 9:15 AM).

<sup>84</sup> See E-mail from Consumer Safety Officer, FDA, to Samia Nasr, et al. (Jan. 28, 2008, 11:39 AM).

anything cleared by OCC” and specifically cited the NECC response draft that CDER had sent to OCC on August 29, 2007.<sup>85</sup>

While discussions about inspecting NECC prior to issuing the response letter were ongoing, on October 9, 2008, FDA’s Los Angeles District Office received a complaint about a patient being hospitalized after having been intravenously administered phosphatidylcholine made by NECC.<sup>86</sup> Phosphatidylcholine injections are mesotherapy products, which FDA had concerns about NECC making and distributing prior to any adverse event reports having been received. According to the complaint report, after the initial infusion period, the patient “developed [a] burning sensation” and a “swollen arm and hand.”<sup>87</sup> After the patient was discharged, he could not swallow food or liquid, vomited, and urinated blood.<sup>88</sup> He was “admitted to an emergency room three more times” and “[t]he physician found blood clots in his arm and hand.”<sup>89</sup> FDA collected a sample “to be analyzed for microbiological analysis and analyzed for potency and chemical contamination.”<sup>90</sup> The NWE-DO was informed about the situation on October 16, 2008. On October 17, Mr. Shamsi emailed the District compliance officer responsible for NECC stating, “We need to make sure the investigator follows up on this.”<sup>91</sup> However, according to the compliance officer’s notes from a meeting that took place two days prior, involving officials from CDER, OCC, and the NWE-DO, including Mr. Shamsi, it had already been decided that “OCC will get a response letter to the firm before we do an inspection.”<sup>92</sup>

On October 31, 2008, more than four years after the underlying inspection and almost two years after NECC responded to the Warning Letter, OCC finally signed off on FDA’s response. The letter “acknowledge[d] and apologize[d] for the significant delay in this correspondence.”<sup>93</sup> Like the agency detailed in the Warning Letter, FDA presented an extensive summary of its authority over compounded drugs and the factors the agency would consider in determining whether to exercise enforcement discretion. FDA concluded by stating, “We agree that the length of intervening period was unusual. This in no way diminishes our serious concerns about your firm’s operation. Your firm must promptly correct the violations noted in the December 4, 2006, Warning Letter, and establish procedures to assure that such violations do not occur. Its failure to do so may result in enforcement action including seizure of the firm’s products and/or an injunction against the firm and its principals. In a future inspection, we will confirm the commitments that you made in your response. We also will verify that your firm’s compounding practices are consistent with the policy articulated in the [2002] CPG, and that your firm’s operation is not otherwise at odds with the conditions under which the agency exercises enforcement discretion towards pharmacy compounding.”<sup>94</sup> FDA, however, never

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<sup>85</sup> E-mail from Samia Nasr to Consumer Safety Officer, FDA, (Jan. 28, 2008, 11:45 AM). *See also* E-mail from Samia Nasr to Consumer Safety Officer, FDA (Jan. 28, 2008, 12:12 PM).

<sup>86</sup> See FDA, CONSUMER COMPLAINT/INJURY REPORT, at 1 (Oct. 9, 2008).

<sup>87</sup> *Id.*

<sup>88</sup> *See id.*

<sup>89</sup> *Id.*

<sup>90</sup> *Id* at 3.

<sup>91</sup> E-mail from Mutahar Shamsi to Compliance Officer, New England Dist. Off., FDA (Oct 17, 2008, 7:11AM).

<sup>92</sup> Memo of Meeting, Compliance Officer, New England Dist. Off., FDA (Oct. 15, 2008).

<sup>93</sup> Letter from Compliance Officer, New England Dist. Off., FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, at 1 (Oct. 31, 2008).

<sup>94</sup> *Id.* at 4.

returned to the firm until the 2012 meningitis outbreak, despite receiving new complaints about NECC's products and practices.

*C. After Closing Out the 2006 Warning Letter, FDA Continues to Receive New Complaints About the Safety of NECC Products and the Company's Practices*

Now that FDA's response to NECC had been sent, based on communications among FDA staff, there should have been no barrier to FDA conducting an inspection of NECC, especially in light of the additional issues and complaints that had been brought to the agency's attention while it worked on a response to NECC's January 2007 letter. On November 4, 2008, however, Mr. Shamsi informed the Director of the NWE-DO Investigations Branch at the time that "CDER would like us to hold off for now" on the inspection that would have covered issues relating to mesotherapy products and general compounding practices.<sup>95</sup> No explanation for this new delay is apparent from the documents produced to the Committee, although FDA staff resumed its debate in February 2009 when the results from the tests of the phosphatidylcholine associated with the hospitalization in California had come back showing the samples were superpotent and displayed signs of degradation.<sup>96</sup>

With further evidence that NECC's practices were continuing to result in unsafe products, FDA finally seemed prepared to take decisive action. On February 11, 2009, after receiving the test results, the same District compliance officer emailed a number of his colleagues, "CDER wants us to immediately (today) go [to] NECC to determine if the firm is willing to recall the Phosphatidyl choline [sic] injection it compounds. The drug is superpotent and not approved and should be recalled. We want to determine the batch size, and where distributed. The recall part should be done immediately and can be separate from the inspection."<sup>97</sup>

Based on a review of the documents, however, it does not appear as though a recall ever happened. According to a memorandum dated February 17, 2009, a conference call was held with CDER and NWE-DO staff. This memorandum indicates that NECC had yet to be informed about the results of the phosphatidylcholine sample.<sup>98</sup> Apparently, FDA had decided to wait and inform NECC of the test results during an inspection, which was scheduled to take place "around March 23, 2009."<sup>99</sup> On March 18, however, Ms. Nasr once again informed the District compliance officer to "hold off [on] the inspection."<sup>100</sup> Ms. Nasr explained that she had spoken with OCC and that "she is working on an inspection assignment to cover 503A and [the] CPG so [we] don't have to do 2 inspections."<sup>101</sup> According to the District compliance officer, Ms. Nasr

<sup>95</sup> E-mail from Mutahar Shamsi to Michael Kravchuk, et al. (Nov. 4, 2008, 4:30 PM).

<sup>96</sup> Jan 30, 2009, memo from Dunn to Nasr.

<sup>97</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi, et al. (Feb. 11, 2009, 7:39 AM).

<sup>98</sup> See DRAFT Memo of Conference Call, Compliance Officer, New England Dist. Off., FDA, *New England Compounding Center Inspection* (Feb. 17, 2009).

<sup>99</sup> *Id.* at 1.

<sup>100</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Investigator, New England Dist. Off., FDA (March 18, 2009, 11:28 AM).

<sup>101</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Investigator, New England Dist. Off., FDA, et al. (March 19, 2009, 9:25 AM).

“said she is afraid if [the] inspection [is] outside [the] 5<sup>th</sup> District [the] firm will file [a] petition against [the] FDA.”<sup>102</sup> It is apparent from this email and additional documents produced to the Committee that in anticipation of having to defend an enforcement action—such as a seizure of products or injunction against the firm—in court, FDA wanted to ensure that observations during an inspection not only addressed the factors listed in the CPG but clearly established that NECC fell outside the safe harbor provided to traditional compounding pharmacies under section 503A.

FDA has confirmed to the Committee that no further inspection of NECC occurred until after the meningitis outbreak had commenced. Towards the end of 2009, FDA received complaints about NECC’s solicitation and distribution of erythromycin without patient-specific prescriptions<sup>103</sup> and NECC’s sale of sodium tetradecyl sulfate to a physician in North Carolina for use in treating varicose veins, when there was only one commercially available product indicated for such treatment.<sup>104</sup> According to this last complaint report, CDER was aware of “NECC compounding sodium tetradecyl sulfate and will be issuing an assignment for NECC in the future.”<sup>105</sup> One year later, in September 2010, Ms. Nasr was informed by an individual with CDER’s Drug Shortage Program about NECC soliciting a certain antibiotic during a shortage, along with a number of other products. This individual stated, “[D]on’t know if there is anything that can be done but thought I would forward it on.” Ms. Nasr replied, “Yes, NECC is under our radar.”<sup>106</sup>

Based on a review of the documents produced to the Committee, the next complaint associated with NECC was one discussed at some length during the November 2012 hearing with Commissioner Hamburg. On May 10, 2011, FDA’s Denver District Office informed the NWE-DO about a Cease and Desist Order the Colorado Board of Pharmacy issued to NECC “regarding their illegal distribution of compounded drugs to hospitals in the Denver metropolitan area.”<sup>107</sup> When Ms. Nasr was made aware of this information on May 11, she forwarded it to others in CDER stating, “Good news.”<sup>108</sup>

The same day FDA’s Denver District Office informed the New England office of the Cease and Desist Order, the New England District compliance officer responsible for NECC spoke to an optometrist with the U.S. Department of Veterans Affairs who was inquiring about whether they could use NECC to repack Avastin for them into single dose units. This communication is significant, because it once again confirms that FDA understood that NECC was acting more like a manufacturer than a traditional compounding pharmacy. He forwarded a summary of his conversation to Ms. Nasr, copying several of his colleagues, one of whom responded, “I didn’t think they could use firms if profiles were unacceptable? NECC Framingham is profiled as a manufacturer (because we determined they are a manufacturer not a

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<sup>102</sup> *Id.*

<sup>103</sup> See E-mail from Redaction to Samia Nasr (Sept. 14, 2009, 3:26 PM). See also E-mail from Samia Nasr to Anderson, et al. (Sept. 14, 2009, 3:34 PM).

<sup>104</sup> See E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr, et al. (Sept. 29, 2009, 6:27 AM).

<sup>105</sup> FDA, CONSUMER COMPLAINT/INJURY REPORT, at 3 (Sept. 17, 2009).

<sup>106</sup> E-mail from Samia Nasr to Associate Dir., CDER Drug Shortage Program (Sept. 14, 2010, 2:44 PM).

<sup>107</sup> E-mail from Senior Case Review Expert, Denver Dist. Off., FDA, to Supervising Consumer Safety Officer, New England Dist. Off., FDA, et al. (May 10, 2011, 4:19 PM).

<sup>108</sup> E-mail from Samia Nasr to Kathleen Anderson, et al. (May 11, 2009, 6:17 AM).

compounding pharmacy)[.]”<sup>109</sup> The compliance officer replied, “You are right. I didn’t think of profiles. And you are right about the repacking, manufacturing, registering, listing and GMPs. I just spoke to Samia Nasr and she said the same thing about repacking that you did that it[’]s manufacturing and not compounding.”<sup>110</sup>

The understanding FDA had reached with the Massachusetts Board in February 2003 that the State would take the lead in making sure that NECC improved its practices was based on their determination that NECC was operating as a compounding pharmacy. By 2011, FDA was well aware of the fact that this was no longer the case. Though it should have been occurring all along, it was during this time period that communication with the State would have been particularly valuable, as FDA had compiled a list of specific issues and complaints associated with NECC’s practices and products that needed to be addressed. In her written testimony for the November 2012 hearing, Commissioner Hamburg pointed to the fact that “[t]he Massachusetts Board of Pharmacy reinspected NECC in 2011 in response to a letter from the firm indicating that NECC was ‘updating its facility and moving into adjacent space’”; that the “inspection included a tour of the facility, security review, licensing review, and inspection of NECC’s sterile and non-sterile processing areas”; and that the MBP “found the facility to be ‘Satisfactory’.”<sup>111</sup>

Commissioner Hamburg neglected to mention that by 2011, FDA knew that NECC was operating like a manufacturer and the agency had failed to pass along any information to the Massachusetts Board that would have allowed it to conduct a more informed inspection. The MDPH has asserted to Committee staff that all communications with FDA pertaining to NECC and/or Ameridose have been produced. There is no evidence from any documents produced to the Committee that FDA even knew the State inspection was taking place. Further, in the same section of inspection notes from which Commissioner Hamburg quoted, the Massachusetts Board inspector stated that he left a voicemail for Mr. Cadden on April 22, 2011, prior to the inspection taking place; that Mr. Cadden called him back on April 28 “pushing off” the inspection by two weeks; and that it was ultimately conducted on May 24, 2011—giving NECC more than a month to prepare.<sup>112</sup> Given that NECC employees were allegedly instructed to drop everything and clean after the firm’s management became aware that FDA would be inspecting the facility in connection with the meningitis outbreak, Mr. Cadden’s actions are concerning.<sup>113</sup>

On July 16, 2012, FDA’s Denver District Office again reached out to the NWE-DO, this time informing them that NECC had violated the Colorado Board of Pharmacy’s Cease and Desist Order. The same compliance officer told his colleague that he would “forward this to CDER to see if they want us to do anything.”<sup>114</sup> He continued: “OCC at the moment is not

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<sup>109</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA, et al. (May 11, 2011, 11:02 AM).

<sup>110</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA, et al. (May 11, 2011, 11:13 AM).

<sup>111</sup> Hamburg Statement, *supra* note 3.

<sup>112</sup> MASS. DEP’T OF PUB. HEALTH, INSPECTION REPORT, at 9 (May 24, 2011).

<sup>113</sup> See *60 Minutes. Lethal Medicine.* (CBS television broadcast Mar. 10, 2013) (transcript available at [http://www.cbsnews.com/8301-18560\\_162-57573470/lethal-medicine-linked-to-meningitis-outbreak/?pageNum=4](http://www.cbsnews.com/8301-18560_162-57573470/lethal-medicine-linked-to-meningitis-outbreak/?pageNum=4)).

<sup>114</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (July 17, 2012, 8:19 AM).

doing anything with compounding pharmacies because of the recent losses in the southwest. . . . CDER said last year we may do something at the end of this year with compounding pharmacies. I recently had a meeting with OCI [FDA's Office of Criminal Investigations] based on a complaint they received and they may be doing something with Ameridose. I invited CDER to the meeting and they were on the speakerphone. They did not want us going to the firm.”<sup>115</sup>

Three things are apparent from this email: 1) FDA continued to grapple with the implications of the Circuit Court split several years after the Fifth Circuit decision in *Medical Center Pharmacy*, and until agency officials agreed on a path forward, oversight would be minimal; 2) the relationship between NECC and Ameridose was well understood by FDA staff; and 3) the complaints about NECC’s sister company, Ameridose, were serious in nature and magnified those already made about NECC. Part IV of this memorandum addresses these points.

#### PART IV: OVERSIGHT OF NECC’S SISTER COMPANY, AMERIDOSE: 2006 – 2012

Like NECC, its sister company, Ameridose, had a significant history with FDA. FDA was well aware of the firms’ shared ownership and management. On several occasions, this factored into FDA’s decision-making about whether and when to take certain actions related to one of the companies. As FDA’s actions pursuant to the meningitis outbreak indicate, a recent inspection of one firm may very well have triggered an inspection of the other.

As Part IV will detail, from an enforcement perspective, FDA’s inaction with respect to Ameridose may be even more egregious than in the case of NECC. Ameridose was different from NECC in one, fundamental way: it had registered with FDA as a manufacturer and repackager of drug products. Ameridose’s website states that the company is “[a]n FDA registered manufacturer” that meets both U.S. Pharmacopeia (USP) compounding standards and current good manufacturing practice (cGMP) requirements.<sup>116</sup> In addition to being registered with FDA, the firm was also registered in Massachusetts as a retail pharmacy and had Drug Enforcement Administration licenses as a manufacturer and retail pharmacy for controlled substances.<sup>117</sup> According to FDA, Ameridose first registered with the agency in September 2006.<sup>118</sup>

##### *A. After Two Inspections Reveal Problems at Ameridose, FDA’s Plan to Issue a Warning Letter to the Company is Ultimately Rejected.*

Within a year of the company having registered with FDA, the agency “received a report through its MedWatch system alleging Ameridose is engaged in the manufacture of unapproved

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<sup>115</sup> *Id.*

<sup>116</sup> <http://www.ameridose.com/about-ameridose/>.

<sup>117</sup> FDA, ESTABLISHMENT INSPECTION REPORT, at 1 (Jan. 22, 2008) [hereinafter, “Jan. 22, 2008, ESTABLISHMENT INSPECTION REPORT”].

<sup>118</sup> See Memorandum from FDA to Committee staff, *Timeline of FDA Interactions with NECC and Ameridose*, at 2 (produced to Committee staff on Feb. 1, 2013, per request of Oct. 12, 2012) [hereinafter, “FDA Timeline”].

intravenous solutions that are not dispensed pursuant to a prescription.”<sup>119</sup> The complainant who filed the MedWatch report asked FDA to investigate and “determine whether this company is making these products on a sound basis, or whether, as I strongly suspect, they are ignoring cGMPs when preparing these intravenous products. I fear a large-scale epidemic of serious infections may occur caused by these products.”<sup>120</sup>

At the same time FDA was examining an NECC complaint forwarded by an anonymous sender, on May 22, 2007, CDER issued an inspection request to the New England District Office for Ameridose. Since FDA’s reply to NECC’s response to the December 2006 Warning Letter was still pending, NWE-DO staff asked whether this would be an impediment to the Ameridose inspection. Samia Nasr, then-Team Leader of CDER’s Compounding Team, informed the primary compliance officer in the District that CDER was “aware of the relationship between NECC and Ameridose” and that they still wanted to proceed with the inspection.<sup>121</sup> According to the draft inspection request for Ameridose, the goal of the assignment was “to obtain current information about the firm’s compounding practices, especially as they relate to the compounding of injectable medications.”<sup>122</sup>

Despite having drafted an inspection request in May, by September 2007, the FDA inspection of Ameridose had yet to occur. Steven Silverman, then-Assistant Director of CDER’s Office of Compliance, emailed Michael Rogers, then-Director of the Division of Field Investigations in FDA’s Office of Regulatory Affairs, and Michael Chappell, then-Acting Associate Commissioner for Regulatory Affairs, a list of the “inspections that are the most critical.”<sup>123</sup> Mr. Silverman suggested that these inspections had been stalled and noted the impact that failing to inspect could have on the public health. He requested “[a]ny help that you or others can provide in breaking these assignments loose” and stated that “[t]hese are all matters for which we’re prepared to take enforcement action and moving them forward will directly benefit public health.”<sup>124</sup> Mr. Silverman listed six “compounding inspection assignments”—Ameridose was second on the list.<sup>125</sup>

The Ameridose inspection finally took place in December 2007, though not before additional concerns about the firm’s practices were reported to FDA. On November 21, 2007, a representative from the Ohio Board of Pharmacy forwarded CDER a solicitation that Ameridose had sent to hospitals in his State. The Ohio Board representative noted the link between Ameridose and NECC stating, “I have a company named Ameridose (which appears to be a subsidiary or an associate of New England Compounding Center – same or similar corporate officers) who is offering to sell pre-filled syringes to hospitals . . . who have purchased . . .

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<sup>119</sup> Inspection Request from Staff Fellow, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk, Dir., Investigations Branch, New England Dist. Off., FDA, at 1 (May 21, 2007) [hereinafter, “May 21, 2007, Inspection Request”].

<sup>120</sup> FDA, MEDWATCH REPORT, at 2 (May 2, 2007).

<sup>121</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Drug Pre-approval Manager, New England Dist. Off. (June 7, 2007, 11:49 AM).

<sup>122</sup> May 21, 2007, Inspection Request, *supra* note 119.

<sup>123</sup> E-mail from Steven Silverman to Michael Rogers, Dir., Div. of Field Investigations, Off. of Reg. Affairs, FDA, et al. (Sept. 5, 2007, 4:52 PM).

<sup>124</sup> *Id.*

<sup>125</sup> *Id.*

infusions pumps.”<sup>126</sup> He concluded, “[T]his appears to be just another episode of drug manufacturing being self-classified as compounding in order to make everything appear to be legitimate.”<sup>127</sup> After several exchanges with an individual in CDER’s Division of Drug Information, the representative from the Ohio Board informed the CDER employee, “I had a conversation with a Greg Conigliaro from Ameridose on Wednesday after I sent you the message. I think he said he was the President of Ameridose. . . . He said that Ameridose, of course, thinks that their preparation of syringes for use in these pumps is perfectly legal. I told him I didn’t think so unless he did it on a patient specific basis by prescription. That did not make him happy[.]”<sup>128</sup> These exchanges were forwarded to Ms. Nasr and others in CDER.

Several days before the Ameridose inspection began on December 7, 2007, CDER raised the company’s connection with NECC and asked the inspector in the NWE-DO to obtain information during the inspection to “elaborate on their business relationship/model and leadership structure and anything else that may potentially cause some inspectional hurdles.”<sup>129</sup> The inspection report that was ultimately filed, however, did not address the question of the companies’ relationship in any depth, other than to list Ameridose’s management structure. The inspection report revealed that Ameridose was engaged in manufacturing activities in that the firm had “made over 610 Lots of products and 38 batches of products of Admixtures for hospitals and packaged them into IV bags, syringes, and vials since they opened in 2006.”<sup>130</sup> This finding prompted an employee on the Compounding Team in CDER to email the Director of the NWE-DO Investigations Branch on March 3, 2008, and request an inspection, stating that “the scope and nature of Ameridose’s activities are outside the bounds of traditional pharmacy practice and more consistent with that of a drug manufacturer. Therefore, as per our conversation today we would like The District to do a full GMP inspection of Ameridose LLC as soon as possible.”<sup>131</sup>

This second inspection of Ameridose did not begin until four months later, in July 2008. In the meantime, the Ohio Board of Pharmacy again reached out to CDER about Ameridose on May 12, this time regarding other sterile injectable products. The Executive Director of the Board stated, “Before the Board issues a Cease & Desist letter to [Ameridose], telling them to stop shipping manufactured products into Ohio under the guise of compounding, I wonder if you could verify for me whether or not this is a legitimately manufactured product that is made by an FDA approved manufacturer?”<sup>132</sup> No substantive reply to this email was produced to the Committee, though the email was forwarded to Ms. Nasr, at which point she notified several of her colleagues that “Ameridose is a pharmacy that we inspected recently and we are waiting for the District to go back for GMP re-inspection.”<sup>133</sup>

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<sup>126</sup> E-mail from Redaction to CDER DRUG INFO (Nov. 21, 2007, 2:02 PM).

<sup>127</sup> *Id.*

<sup>128</sup> E-mail from Redaction to CDER DRUG INFO (Nov. 23, 2007, 12:55 PM).

<sup>129</sup> E-mail from Reg. Operations Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Drug Pre-Approval Manager, New England Dist. Off., FDA (Dec. 4, 2007, 10:55 AM).

<sup>130</sup> Jan. 22, 2008, ESTABLISHMENT INSPECTION REPORT, *supra* note 117.

<sup>131</sup> E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk (Mar. 3, 2008, 3:27 PM).

<sup>132</sup> E-mail from Exec. Dir., Ohio St. Bd. of Pharmacy, to CDER DRUG INFO (May 12, 2008, 1:49 PM).

<sup>133</sup> E-mail from Samia Nasr to Kathleen Anderson, et al. (July 16, 2008, 9:15 AM).

FDA began its second inspection of Ameridose on July 21, 2008. According to the inspection report, Ameridose had been labeled a “High Risk facility” in advance. Since the previous inspection only seven months before, Ameridose’s operations had considerably expanded. The report stated, “The firm currently markets over 600 products including 7 Antibiotic class, 15 Class II, 1 Class III, 2 Class IV and many Class VI products”<sup>134</sup> and that their customers include “approximately 500 Hospital Pharmacies located in 49 of the 50 states.”<sup>135</sup> Summarizing the firm’s operations, the FDA inspector stated, “The firm ships 75% of their product outside of Massachusetts. [Ameridose] stated that all their customers that order the products are affiliated with hospitals. The firm manufactures small orders in Lot sized batches and combines multiple orders of one specific product into Batches of finished product. None of their manufactured or repackaged products are linked to a specific patient prescription.”<sup>136</sup>

In addition to concerns about the nature of the company’s operations, the FDA inspector also observed several objectionable practices in Ameridose’s facility that were then documented in a Form 483 that FDA issued to the company on August 6, 2008. While all were troubling, the first observation was particularly egregious. According to the Form 483, Ameridose was not waiting to receive test results confirming the strength or sterility of their products before shipping them to customers. Specifically, the Form 483 stated, “Testing and release of drug product for distribution [does] not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.”<sup>137</sup> Further, FDA found that there was “no potency or identity test done on the finished drug product, and the product is shipped immediately and prior to the 14 day sterility test results are received by the firm.”<sup>138</sup> One example provided by the inspector was fentanyl, a narcotic injectable many times more potent than morphine. The inspector retained samples of this product for testing.<sup>139</sup>

Several individuals in the NWE-DO were alarmed by the Ameridose inspection findings. After reviewing the report, one compliance officer emailed her colleague in the District: “This case bothers me the more I think of it. . . . [T]he firm doesn’t conduct potency testing on ANY finished product (only the stock solution, which they subsequently dilute) so I have serious concerns with the potency [of] all their products. Perhaps we should be thinking of getting a health hazard evaluation and getting the firm to recall as many of their products as we can or going out to get more finished product samples. A vast majority of their products are sterile injectable opioids, super potency is a serious concern.”<sup>140</sup>

By September 10, 2008, the results from the fentanyl samples showed that the product was, in fact, superpotent.<sup>141</sup> The following day, a compliance officer in the NWE-DO informed

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<sup>134</sup> FDA, ESTABLISHMENT INSPECTION REPORT, at 4 (Aug. 22, 2008) (page numbers correspond with narrative report attachment).

<sup>135</sup> *Id.* at 5.

<sup>136</sup> *Id.* at 3.

<sup>137</sup> FDA, AMERIDOSE LLC FORM FDA 483, at 1 (Aug. 6, 2008).

<sup>138</sup> *Id.*

<sup>139</sup> See FDA Timeline, *supra* note 118.

<sup>140</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (Sept. 9, 2008, 7:23 PM).

<sup>141</sup> See E-mail from Compliance Officer, New England Dist. Off., FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA (Sept. 10, 2008, 9:31 AM).

Sophia Pasedis, the Vice President of Regulatory Affairs at Ameridose, about the results. According to a memorandum of the telephone call, the compliance officer told Ms. Pasedis that “FDA is very concerned” and asked what Ameridose was “going to do with the product in the market.”<sup>142</sup> According to a memorandum of the conversation, “She said she was going to call her accounts to see if there were any reactions and if there was any product out there. I told her if she was going to [do a] voluntary recall she could call our recall coordinator. She said she would like to first make some calls and then she would call me back.”<sup>143</sup> Ms. Pasedis did call him back and, according to the compliance officer, “[She] said 155 bags were made and sent to 5 different facilities. She said all the facilities have ordered the product multiple times. She said one firm ordered 100 bags. She did not think she had to do anything further.”<sup>144</sup> When he informed her that Ameridose should consider issuing a recall notice, “She said she could not make a decision until she speaks with one of her bosses and none are answering their cell phones.”<sup>145</sup> After stating that he informed Ms. Pasedis they needed to speak first thing in the morning, the compliance officer concluded his memorandum: “The person[ ] did not appear to know what a recall is and we may have problems tomorrow. . . .”<sup>146</sup>

On September 12, FDA spoke with Gregory Conigliaro, co-owner of Ameridose. According to the FDA memorandum summarizing this telephone call, the compliance officer “told Mr. Conigliaro that it was his responsibility as a manufacturer to manufacture a safe and effective product. [He] told Mr. Conigliaro the product fails potency and his product is now adulterated. . . . Mr. Conigliaro said he would do the right thing and send the recall notification to the 5 accounts.”<sup>147</sup> The recall was conducted that day.<sup>148</sup> On September 15, 2008, the recall notice was sent to Michael Levy, who succeeded Steven Silverman as the Director of the DNDLC in CDER’s Office of Compliance. He stated in response, copying Samia Nasr and Kathleen Anderson, “Thanks. We have a history with this firm. . . . Maybe it’s time for reinspection and possible follow up enforcement action?”<sup>149</sup> During this time period, Mr. Levy was also engaged in discussions about the NECC inspection being considered. On September 19, Samia Nasr emailed him and noted the firms’ relationship, stating, “Please remember that [A]meridose and NECC are owned by two brothers.”<sup>150</sup>

Even prior to the fentanyl recall, based on observations included in the August 2008 inspection report and corresponding Form 483, CDER had already made the determination that a Warning Letter should be sent to Ameridose and that it “should include both new drug cha[r]ges

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<sup>142</sup> Memo of Telephone Conversation between Compliance Officer, New England Dist. Off., FDA, and Sophia Pasedis, Vice President of Reg. Affairs, Ameridose LLC (Sept. 11, 2008).

<sup>143</sup> *Id.*

<sup>144</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Recall Coordinator, New England Dist. Off., FDA (Sept. 11, 2008, 5:12 PM).

<sup>145</sup> *Id.*

<sup>146</sup> *Id.*

<sup>147</sup> Draft Memo of Telephone Call between Compliance Officer, New England Dist. Off., FDA, and Gregory Conigliaro, Co-owner, Ameridose (Sept. 12, 2008).

<sup>148</sup> See E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi, et al. (Sept. 12, 2008, 10:34 AM).

<sup>149</sup> E-mail from Michael Levy, Dir., DNDLC, Off. of Compliance, CDER, FDA, to Rick Friedman, Dir., Div. of Manufacturing & Product Quality, Off. of Compliance, CDER, FDA (Sept. 15, 2008, 8:40 PM).

<sup>150</sup> E-mail from Samia Nasr to Michael Levy (Sept. 19, 2008, 7:28 AM).

and GMP charges.”<sup>151</sup> According to the documents, CDER reviewed the NWE-DO’s draft Warning Letter for several months and ultimately cleared it for Chief Counsel’s Office review in February 2009. Before it was cleared, there were a number of discussions among CDER officials about the nature of Ameridose’s operations and how they would impact potential enforcement actions. For example, after reviewing the latest draft of the Warning Letter on January 23, 2009, Michael Levy asked his Deputy, Kathleen Anderson, whether Ameridose was “a hospital outsourcer like CAPS [Central Admixture Pharmacy Services]? If so, haven’t we avoided bringing new drug charges against these firms?”<sup>152</sup> Ms. Anderson replied, “Yes, it appears to be a type of outsourcer, but Ameridose has several important differences. We haven’t brought new drug charges against outsourcers that are manipulating/reconstituting FDA approved drugs as a hospital pharmacy typically does and that are not making copies of FDA approved drugs. Ameridose on the otherhand [sic] is using bulk APIs to make stock solutions of their own versions of drugs, including many that are copies of approved drugs.”<sup>153</sup> Levy responded, “OK, got it. Thanks.”<sup>154</sup>

On March 4, 2009, one of the lawyers in the Chief Counsel’s Office informed CDER and the NWE-DO that they would approve the Warning Letter to Ameridose, but that “OCC’s clearance is on hold pending . . . a final determination as to whether clarifications are needed” to a paragraph discussing FDA’s enforcement policy with respect to entities located outside the Fifth Circuit.<sup>155</sup> This issue had yet to be resolved six months later, at which point CDER made the decision to disapprove the Warning Letter on September 1, 2009.<sup>156</sup> When the NWE-DO compliance officer responsible for Ameridose informed Mutahar Shamsi, then-Director of Compliance in the NWE-DO, of the decision, he noted the impact that the Circuit Court split and the resulting delay had on FDA’s willingness to issue a Warning Letter to Ameridose, stating, “The activity notes say the [Warning Letter] case was put on hold due to conflicting court rulings related to Pharmacy Compounding and CDER is not proceeding with issuance of this [Warning Letter] because it has now been 1 year since the district[’]s inspection of the firm.”<sup>157</sup>

Angered by the news that the Warning Letter would not be issued because CDER and OCC could not agree on a path forward, Mr. Shamsi emailed Alyson Saben, FDA’s Deputy Director of Enforcement, and other officials in the agency, asking whether they could discuss the decision and stating, “NWE-DO spent a lot of time developing this case last year and having it ‘closed’ for nebulous reasons is troubling. . . . This is quite frustrating since I thought we had a good [Warning Letter]. I’ve told our [Investigations Branch] to not bother inspecting compounding pharmacies if we aren’t going to act on the violations.”<sup>158</sup> Ms. Saben forwarded

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<sup>151</sup> E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (Sept. 9, 2008, 11:00 AM).

<sup>152</sup> E-mail from Michael Levy to Kathleen Anderson, Dep. Dir., DNDLC, Off. of Compliance, CDER, FDA (Jan. 23, 2009, 10:21 PM).

<sup>153</sup> E-mail from Kathleen Anderson to Michael Levy (Jan. 24, 2009, 7:53 AM).

<sup>154</sup> E-mail from Michael Levy to Kathleen Anderson (Jan. 24, 2009, 9:55 AM).

<sup>155</sup> E-mail from General Attorney, Office of the Chief Counsel (OCC), FDA, to Michal Levy, et al. (Mar. 4, 2009, 5:49 PM).

<sup>156</sup> See E-mail from Div. of Info. Resources Mgmt. to Compliance Officer, New England Dist. Off., FDA, et al. (Sept. 1, 2009, 11:13 AM).

<sup>157</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi (Sept. 1, 2009, 11:27 AM).

<sup>158</sup> E-mail from Mutahar Shamsi to ORA DCB Advisory Comm. (Sept. 1, 2009, 11:52 AM) (emphasis added).

Mr. Shamsi's email to Michael Levy, copying Deborah Autor and others in CDER. She stated, "As I recall . . . CDER was moving forward with developing a prioritized list of ongoing/open pharmacy compounding cases for which we are prepared to move forward/refresh the evidence in light of [then-Acting Commissioner of FDA] Dr. Sharfstein's decision to proceed with 503A. At that time, we discussed that CAPS [Central Admixture Pharmacy Services], Phar[MED]ium and Ap[o]the[C]ure were on the short list. Could you provide us with a status check on your current thinking and what this means for other cases such as Ameridose?"<sup>159</sup>

After hearing about the decision on Ameridose, Douglas Stearn, then-Director of the Division of Compliance Policy in FDA's Office of Enforcement, reached out to Mr. Shamsi on September 2, and indicated that FDA might be prepared to initiate enforcement actions against compounding operations. Mr. Stearn stated, "CDER is changing on this issue. Now is an ideal time to push."<sup>160</sup> The next day, Mr. Stearn emailed Michael Levy and Kathleen Anderson and noted, "There are a number of districts that have voiced concerns about some compounders that had previous OAI [Official Action Indicated] inspections. One thing that I have heard is that some of these compounders have serious sterility issues, which I understand . . . *CDER sees as a central public health issue*. It seems to me these districts would welcome the opportunity to work with CDER on choosing and focusing on compounding firms that have the issues CDER has identified."<sup>161</sup>

FDA's indecision about how to address compounding operations in light of the Fifth Circuit's decision in *Medical Center Pharmacy* significantly deterred enforcement actions against companies, including Ameridose, even when the agency knew they were engaged in manufacturing and jeopardizing public health in the process.

#### *B. From 2009-2012, FDA Fails to Take Action While Complaints about Ameridose's Products and Practices Continue to Mount*

It is apparent from documents produced to the Committee that senior officials at FDA were discussing how to address growing concerns about Ameridose and similar companies while also grappling with what the Fifth Circuit's decision to uphold the non-speech related provisions of section 503A meant for the agency. FDA considered at length whether the agency should apply section 503A only in the Fifth Circuit and continue to exercise enforcement discretion elsewhere, or whether it should uniformly apply section 503A nationwide, except in the Ninth Circuit, where the agency would exercise enforcement discretion regarding compounding that satisfies the criteria in section 503A. While the agency has since asserted that the former course

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<sup>159</sup> E-mail from Alyson Saben, Dep. Dir., Off. of Enforcement, Off. of Reg. Affairs, FDA, to Deborah Autor, et al. (Sept. 2, 2009, 12:11 PM). On February 10, 2012, the Department of Justice, at the request of FDA-OCI, charged AphotheCure Inc., a company located in Dallas, TX, with two misdemeanor criminal violations of the FDCA in connection with their interstate shipment of two lots of misbranded injectable products that led to the deaths of three people in 2007. After the meningitis outbreak, in February and March 2013, FDA inspected four PharMEDium Services, LLC facilities, and four CAPS facilities, issuing Form 483s in each instance. See <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm340853.htm>.

<sup>160</sup> E-mail from Douglas Stearn, Dir., Div. of Compliance Policy, Off. of Enforcement, Off. of Reg. Affairs, FDA, to Mutahar Shamsi, et al. (Sept. 2, 2009, 4:17 PM).

<sup>161</sup> E-mail from Douglas Stearn to Kathleen Anderson, et al. (Sept. 3, 2009, 8:54 AM) (emphasis added).

of action would be followed, based on a review of the documents, it is apparent that FDA ultimately made the decision to pursue the latter. Prior to formally announcing this new agency position, however, FDA determined that new guidance and regulations needed to be drafted to provide a clear framework that FDA would use to differentiate between pharmacy compounding and drug manufacturing—a process that was still ongoing several years later and which was almost completed at the time of the fungal meningitis outbreak in September 2012. Unfortunately, enforcement actions stalled while the agency debated whether and how to conduct inspections or bring actions against compounding operations in the interim.

Meanwhile, CDER and NWE-DO staff was becoming increasingly concerned about Ameridose. On October 27, 2009, CDER received an anonymous email from an informant within the company: “July/August 2008 the FDA came to Ameridose LLC in [F]ramingham, [MA] for an inspection. The company performed illegal and unethical actions. They directed the testing facilities they use to change reports, based on the drug[ ] results. They forged documents, forced employees to direct others to do so. . . . [Gregory Conigliaro] silently directs people to change results, doctor the findings but hides in his office. . . . VP is Sophia Pasedis, Pharm D all licenses are in her name, she too is frauduelent [sic].”<sup>162</sup> FDA’s Office of Criminal Investigations (OCI) ultimately forwarded the email to Mutahar Shamsi on December 7, who replied, copying Samia Nasr, “Thanks for the info. We are waiting for an assignment from CDER to go out and will follow up on this. Ameridose has been on our radar for quite some time.”<sup>163</sup>

Based in part on this complaint, FDA documents demonstrate that the agency was preparing to inspect Ameridose, though the inspection would again be delayed. After further discussing the informant’s claims with Ms. Nasr over the telephone, Mr. Shamsi emailed several individuals in the NWE-DO and OCI, stating that “CDER will be issuing an assignment for Ameridose after an outsourcing guidance document has been cleared through CDER.”<sup>164</sup> He then decided, “Let’s wait until we get an assignment from CDER before we proceed on our side because if we forward anything down to OCC it will not proceed quickly. Obviously if we get information of an imminent health hazard we’ll have to go out. I don’t see that here yet.”<sup>165</sup>

The documents indicate that CDER did not begin drafting the inspection request until April 2010 and that it was primarily to follow up on the issues raised in the Form 483 and the draft Warning Letter, both of which were based on the previous GMP inspection in 2008.<sup>166</sup> The assignment was received by the NWE-DO on April 28, 2010, though it was not scheduled to take place until July.<sup>167</sup> In the interim, CDER received another new complaint about Ameridose in

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<sup>162</sup> E-mail from druginfo@fda.hhs.gov to CDER DRUG INFO (Oct. 27, 2009, 6:47 PM).

<sup>163</sup> E-mail from Mutahar Shamsi to Resident Agent in Charge, Off. of Crim. Investigations (OCI), FDA, et al. (Dec. 7, 2009, 4:54 PM).

<sup>164</sup> E-mail from Mutahar Shamsi to Compliance Officer, New England Dist. Off., FDA, et al. (Dec. 8, 2009, 11:54 AM).

<sup>165</sup> *Id.*

<sup>166</sup> See E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA to Samia Nasr (Apr. 15, 2010, 2:44 PM).

<sup>167</sup> See E-mail from Investigator, New England Dist. Off., FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA (Apr. 29, 2010, 10:36 AM).

early June that altered the focus of the discussions. This complaint was made by a manufacturer and related to “Ameridose’s pre-mixed nicardipine injection products.”<sup>168</sup>

The new complaint complicated FDA’s previously planned inspection of Ameridose. On July 6, 2010, a member of CDER’s Compounding Team reached out to the primary compliance officer in the District Office informing him that CDER was “still trying to discuss with [the Office of the Chief Counsel] on how to approach the firm” and asking that he keep CDER up to date on whether the state independently “decide[s] to inspect [the] site in regards to the nicardipine.”<sup>169</sup> It is clear from the documents that a decision was made to accompany the State to Ameridose on July 8, but the FDA inspector was told to focus exclusively on the commercial complaint related to the nicardipine injections. According to the FDA inspector’s report, “This inspection did not include review of corrective actions to the previous FDA 483. This was a directed inspection specifically to cover the admixing and distribution of Nicardipine IV.”<sup>170</sup> The inspector’s report and her related comments indicate that she questioned whether Ameridose was in fact a compounding pharmacy, as the assignment referenced. Throughout the report, the inspector used the terms “manufactures” and “manufacturing” and her statement of jurisdiction held that the “firm currently repacks and manufactures prescription drug products which are FDA regulated drug products.”<sup>171</sup> While forwarding her colleague notes from the inspection, the inspector stated, “I was looking on their website to see if they identify themselves as a compounding pharmacy – they don’t. It states in multiple places that they are an FDA registered manufacturer. I didn’t see ‘compounding’ anywhere.”<sup>172</sup>

Soon after the inspection, the NWE-DO received an anonymous complaint from a “pharmacist in the manufacturing department” at Ameridose. The informant specifically raised concerns about the safety of Ameridose products.<sup>173</sup> This individual contacted the District Office about his concerns on at least three separate occasions in July and August 2010. During this initial call, “He explained that he recently became aware of some potential GMP issues and he wanted to bring them to our attention.”<sup>174</sup> According to a memorandum of the call, the informant raised concerns about contamination, stating that “[approximately] a week and a half ago, they were making a batch of succinylcholine. . . . He stated that after a few lots, someone observed particulates in the bag. He stated that they determined the particulates to be ‘angel hair’ and pieces of the bag itself. He stated that he was not sure if the previous lots made from the same batch were released.”<sup>175</sup> According to the related complaint report, it was also the informant’s “opinion that the quality assurance program [had] been downsized and deprioritized.”<sup>176</sup>

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<sup>168</sup> E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA (June 9, 2010, 4:12 PM).

<sup>169</sup> E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (July 6, 2010, 9:10 AM).

<sup>170</sup> FDA, ESTABLISHMENT INSPECTION REPORT, at 1 (July 8, 2010).

<sup>171</sup> *Id* at 3.

<sup>172</sup> E-mail from Investigator, New England Dist. Off., FDA, to Investigator, New England Dist. Off., FDA (July 9, 2010, 2:58 PM).

<sup>173</sup> See Memorandum of Teleconference between Redaction and Compliance Officer, New England Dist. Off., FDA (July 13, 2010).

<sup>174</sup> *Id.*

<sup>175</sup> *Id.*

<sup>176</sup> FDA, CONSUMER COMPLAINT/INJURY REPORT (July 13, 2010).

After the inspection limited to the nicardipine complaint was completed, the District compliance officer responsible for Ameridose asked CDER about the broader inspection assignment that was issued in April and scheduled to begin on July 26, 2010. CDER's response was that it "should be put on hold for now" and that they "need[ed] to resolve the nicardipine issue with the firm first before we do a full inspection."<sup>177</sup>

On June 8, July 7, and at least one more time on July 22, 2010, an attorney for the company who had filed the commercial complaint about Ameridose's nicardipine distribution reached out to Deborah Autor, then-Director of Compliance at CDER, asking why FDA had yet to take any action against Ameridose.<sup>178</sup> On July 23, Ms. Autor forwarded the chain of emails to Kathleen Anderson and Samia Nasr, copying other CDER officials, and asking, "What's your assessment of this situation?"<sup>179</sup> Ms. Anderson replied that the New England District Office had just inspected Ameridose pursuant to the nicardipine complaint but acknowledged there were other issues with the company that needed to be addressed, which would factor into the agency's course of action. She explained, "It is my understanding that Ameridose is a state licensed pharmacy and it's [sic] operation is similar to CAPS. We will determine next steps based on what is found during the inspection, whether the firm is operating outside of 503A and the CPG, what the state plans, and the status of the nicardipine issue, etc."<sup>180</sup>

While this debate ensued within the agency, FDA continued to receive complaints associated with the safety of Ameridose products. On July 23, 2010—the same day of the exchange between Ms. Anderson and Ms. Autor—FDA received a MedWatch report about a nurse administering half of a syringe of dextrose 50% made by Ameridose to a patient before noticing "a white precipitate below the rubber plunger" which "extended about ¾ inch along the plunger's base."<sup>181</sup> No additional details were provided and no related communications were produced to the Committee regarding this complaint. Again, based on the documents produced to the Committee, it appears as though the complaint essentially went unnoticed.

A few weeks later, on August 16, 2010, the Ameridose informant again contacted the NWE-DO but this time raised new and more alarming concerns about Ameridose's practices and their potential impact on the safety of the company's products. At least one of his claims, documented in a District Office memorandum, was shockingly similar to the violations FDA found when it inspected both NECC and Ameridose after the fungal meningitis outbreak began. According to the memorandum, the informant alleged that not only was the Ameridose sales team "assisting in labeling operations in a clean room" but that "one of the 3 clean rooms had a *positive result for mold growth.*"<sup>182</sup> The informant also alleged that Ameridose was tampering with its sampling procedures, stating that the company would "clean the area first before taking

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<sup>177</sup> E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (July 14, 2010, 8:56 AM).

<sup>178</sup> See Letter from Counsel to Deborah Autor (June 8, 2010) and Letter from Counsel to Deborah Autor (July 8, 2010). See also E-mail from Counsel to Deborah Autor (July 22, 2010, 11:28 AM).

<sup>179</sup> E-mail from Deborah Autor to Samia Nasr, et al. (July 23, 2010, 4:32 PM).

<sup>180</sup> E-mail from Kathleen Anderson to Deborah Autor (July 23, 2010, 4:59 PM).

<sup>181</sup> FDA, MEDWATCH REPORT (July 23, 2010).

<sup>182</sup> Memorandum of Teleconference between Redaction and Compliance Officer, New England Dist. Off., FDA, at 1 (Aug. 16, 2010) (emphasis added).

the [environmental] sample[s].”<sup>183</sup> Although the informant admitted that he was not aware of any illnesses or complaints resulting from these activities, he also stated that “he would not be in a position to know this type of information” and some of the information he had provided FDA was second or third hand.”<sup>184</sup> The compliance officer wrote, “I explained that FDA takes complaints such as his very seriously and that we would need to evaluate the information he provided. I asked if he was aware of any other issues that would cause a public health safety concern. He said no, but that he would contact us if he became aware of similar issues. I asked if he contacted any other offices such as the State of MA or the Board of Pharmacy. He stated he had not but would plan on doing so. We discussed that FDA is still seeking jurisdiction over compounding pharmacies.”<sup>185</sup>

The compliance officer sent her memorandum to several of her District Office colleagues, even though it was her understanding that “FDA may not be in a position to follow-up at this time[.]”<sup>186</sup> In an email, the compliance officer specifically asked if they should share the information with the state.<sup>187</sup> This email, along with the memorandum, was forwarded to Samia Nasr in CDER. Ms. Nasr questioned the informant’s claims, stating that she was “not sure about his complaint since he said that this information was second or third hand. What’s this mean? [H]e heard it from someone else? [A]nd I am wondering when he says manufacturing area, does he mean[s] no prescriptions?”<sup>188</sup> The compliance officer responded, “Yes, 2<sup>nd</sup> hand means he heard i[t] from someone else which is unreliable.”<sup>189</sup>

Four days later, on August 20, 2010, the informant contacted the District Office again, this time to provide “additional information regarding the mold finding at Ameridose on 8/5/10.”<sup>190</sup> According to a memorandum of the call, the informant stated that the mold was found in “the hood in which operations took place.”<sup>191</sup> Again, this information was forwarded to Samia Nasr in CDER who, in response, asked the compliance officer, “Would it help if I set up a meeting with OCC to discuss possibility of full inspection?”<sup>192</sup> The compliance officer replied, “I don’t think so because in his second call he stated he is not directly involved with these findings and is obtaining his information from someone at the firm.”<sup>193</sup> Ms. Nasr simply stated, “Ok, thanks.”<sup>194</sup>

Based on documents produced to the Committee, it does not appear that FDA took any steps to investigate or follow up on these claims, nor is there any evidence that FDA referred them to the State. FDA was still determining, though, what it should do in response to the

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<sup>183</sup> *Id.*

<sup>184</sup> *Id.* at 2.

<sup>185</sup> *Id.*

<sup>186</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA, et al. (Aug. 17, 2010, 8:02 AM).

<sup>187</sup> *See id.*

<sup>188</sup> E-mail from Samia Nasr to Compliance Officer, New England Dist. Off., FDA (Aug. 17, 2010, 10:34 AM).

<sup>189</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr (Aug. 17, 2010, 10:42 AM).

<sup>190</sup> Memorandum of Teleconference between Redaction and Compliance Officer, New England Dist. Off., FDA (Aug. 20, 2010).

<sup>191</sup> *Id.*

<sup>192</sup> E-mail from Samia Nasr to Compliance Officer, New England Dist. Off., FDA (Aug. 23, 2010, 11:00 AM).

<sup>193</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr (Aug. 23, 2010, 11:06 AM).

<sup>194</sup> E-mail from Samia Nasr to Compliance Officer, New England Dist. Off., FDA (Aug. 23, 2010, 11:38 AM).

nicardipine situation. On October 15, 2010, the attorney who had previously reached out to Deborah Autor on several occasions emailed her again and expressed his frustration with FDA's failure to take action against Ameridose in regard to the nicardipine complaint. The attorney pointed out that “[i]t has now been more than four months since we called this serious situation to your attention, yet to date we have seen no evidence that the agency has taken any enforcement action to protect patients and preserve the integrity of FDA's drug review and approval system. In the meantime, Ameridose continues to expand its production and distribution of its unapproved drug product, thus increasing the potential risks to patients.”<sup>195</sup>

Three days later, on October 18, 2010, Ms. Autor received an unrelated letter from an attorney representing PharMEDium Services LLC, regarding Ameridose's practices and requesting that the agency “clarify its policies with respect to this category of compounding pharmacies.”<sup>196</sup> PharMEDium's letter makes plain that other companies with large-scale compounding operations were well aware of Ameridose's efforts to skirt regulation and were trying to distance themselves from Ameridose's practices, understanding the impact such practices could have on patient safety. According to PharMEDium's attorney, “A principal issue is whether such compounders may utilize active pharmaceutical ingredients (API) (bulk powders) in lieu of commercially available injectable drug products (sterile vials) from approved new drug manufacturers or registered old drug manufacturers, as starting materials in this process. If those providing compounding services are permitted to do this, it will drastically change the way such preparations are compounded nationwide and *put the manufacture of large quantities of sterile drugs for use in compounding in the hands of those who are not approved or 'regulated' to perform that operation.*”<sup>197</sup> The letter went on to detail Ameridose's compounding practices and—in PharMEDium's view—FDA's inaction in response. It concluded in part, “Ameridose and others starting with bulk API can no longer be considered outsourcers when their compounding operations bear no resemblance to those of a hospital pharmacy, and instead resemble drug manufacturing.”<sup>198</sup>

If there was ever any doubt, by the end of 2010, it should have been abundantly clear to FDA that Ameridose was not operating as a traditional compounding pharmacy. Not only did FDA understand the nature and scope of Ameridose's practices, it was well aware of the dangers they were posing. Based on the documents produced to the Committee, FDA officials reacted as though Ameridose was a nuisance it could not figure out how to resolve, rather than a ticking time bomb.

#### *C. Despite an Increasing Number of Complaints, FDA Decides to Further Delay Action against Ameridose until after New 503A Guidance is Drafted*

While FDA worked to resolve the issues raised by the nicardipine complaint, the agency had effectively tabled conducting a broader inspection of Ameridose to follow up on the concerning observations documented in the previous inspections and to investigate the issues raised by the company informant, among the other complaints. Once FDA was informed on

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<sup>195</sup> E-mail from Counsel to PharMEDium Services LLC to Deborah Autor (Oct. 15, 2010, 4:37 PM).

<sup>196</sup> Letter from Counsel to Deborah Autor, at 1 (Oct. 18, 2010).

<sup>197</sup> *Id.* (emphasis added).

<sup>198</sup> *Id.* at 3.

January 14, 2011, that a settlement had been reached between Ameridose and the commercial complainant in the nicardipine matter,<sup>199</sup> the agency turned its attention to the various other complaints that it had received since the July 2008 inspection and failed to address. After learning of the nicardipine settlement on January 20, Samia Nasr noted that CDER staff was scheduled “to meet with OCC in two weeks to discuss full inspection of Ameridose since we have several complaints regarding its practice.”<sup>200</sup> This February 4, 2011, meeting between representatives from CDER, OCC, and the NWE-DO was the first of several discussions to address the “[c]ompilation of complaints towards Ameridose.”<sup>201</sup> Less than two weeks later, they would have another complaint to add to the list.

A representative from the Institute of Safe Medication Practices (ISMP) informed FDA on February 15, 2011, of an issue ISMP had been made aware of during an ongoing shortage of 23.4% sodium chloride, a common electrolyte replenisher.<sup>202</sup> According to a medication error report, which had been submitted to ISMP’s website with a photocopied Ameridose label, the pharmacist complainant had “great concerns over the safety” of the sodium chloride product.<sup>203</sup> The complainant stated that the “drug is filled into an empty Hospira bag. This bag can be directly attached to any IV line and infused undiluted into a patient. The warning says ‘May need to dilute’. There is no circumstance where this product would not need to be diluted prior to infusion. The commercial product is filled into vials and the cap reads ‘MUST BE DILUTED’. It is not labeled as Sodium Chloride USP, nor does it say that it is sterile. *As a practicing pharmacist, I am shocked that such a product would be allowed to be distributed for use in the United States.*”<sup>204</sup>

The patient safety implications of the latest Ameridose complaint were immediately clear to Michael Levy, then-Director of the DNDLC in CDER’s Office of Compliance. Upon receiving the complaint, he forwarded it Samia Nasr and asked her to have someone look into it, stating that “it should be a priority.”<sup>205</sup> Ms. Nasr responded to Mr. Levy, copying Kathleen Anderson, and informed him that CDER was “trying to get OCC to let us go and inspect Ameridose.”<sup>206</sup>

A member of CDER’s Compounding Team echoed Mr. Levy’s concerns about patient safety to Ms. Nasr. In an email dated February 16, 2011, the Compounding Team member explained the nature of the risk posed, noting that “[t]he 100 ml bags of 23.4% NaCl that Ameridose is compounding [are] *extremely dangerous*. . . . How is Ameridose even obtaining these empty Hospira 100mg bags? The way that these bags appear and are labeled is very misleading. To me it appears that these bags are made by Hospira. . . . And to say that ‘Caution Concentration: may need dilute’ is an understatement. This must be diluted! And they should

<sup>199</sup> See Letter from Counsel to Deborah Autor (Jan. 14, 2011).

<sup>200</sup> E-mail from Samia Nasr to Kathleen Anderson, et al. (Jan. 20, 2011, 1:56 PM).

<sup>201</sup> E-mail from Reg. Operations Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr, et al. (Feb. 4, 2011, 11:07 AM).

<sup>202</sup> See E-mail from President, ISMP, Dir., Div. of Medication Errors Prevention and Analysis, Off. of Surveillance and Epidemiology, CDER, FDA, et al. (Feb. 15, 2011, 9:59 AM).

<sup>203</sup> E-mail from ISMP Mailsender to Pharmacy Technician Analyst, ISMP (Feb. 14, 2011, 5:00 PM).

<sup>204</sup> *Id.* (emphasis added).

<sup>205</sup> E-mail from Michael Levy to Samia Nasr (Feb. 15, 2011, 6:00 PM).

<sup>206</sup> E-mail from Samia Nasr to Michael Levy, et al. (Feb. 16, 2011, 6:13 PM).

further warn that this bag should not be directly infused to the patient. This is unbelievable! *I think this is a disaster waiting to happen.*<sup>207</sup> In a subsequent exchange, Ms. Nasr stated, “Let us see if OCC agrees on inspecting.”<sup>208</sup>

Before OCC could weigh in on the ISMP complaint, ISMP informed FDA later that day that they had reached out to Ameridose and the company had agreed to revise the label.<sup>209</sup> According to the Compounding Team employee who was alarmed by what she had learned earlier in the day, “The labeling looks much better.”<sup>210</sup> While she still had concerns “[g]iven Ameridose’s past history,” she felt as though they could be addressed “when we do a full inspection of the firm in the future.”<sup>211</sup> Whether such an inspection would ever occur, however, was still an open question at the agency.

After a March 4, 2011, discussion about Ameridose between CDER, OCC, and the NWE-DO, an employee on CDER’s Compounding Team sent an email to the group titled, “Reasons to go inspect Ameridose,” which listed many of the concerns FDA had with the company, including its labeling, its lack of patient-specific prescriptions, and its practices as they relate to sterile injectable products.<sup>212</sup> Documents produced to the Committee show that lawyers in the Chief Counsel’s Office were debating which concerns CDER had already detailed could constitute actionable violations under the FDCA, in advance of the full inspection being considered. The debate about whether FDA should even conduct such an inspection of Ameridose, however, would continue throughout the summer of 2011. Finally, on September 15, 2011, a Compounding Team employee emailed others in CDER, noting that they had decided to hold off on the Ameridose inspection. According to this email, FDA would not proceed with an inspection “until we issue the 503A guidance. . . . Plan is to re-inspect Ameridose 6 months after issuance of a 503A guidance.”<sup>213</sup> FDA’s decision to assert its authority under section 503A of the FDCA, except in the Ninth Circuit, was previously touched upon and will be subsequently addressed in greater detail, particularly with respect to the impact it had on FDA’s oversight of NECC and Ameridose.

While FDA turned its attention to working on the 503A guidance, the complaints about Ameridose continued. In fact, on August 9, 2011, a new series of anonymous phone calls from

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<sup>207</sup> E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr (Feb. 16, 2011, 10:01 AM) (emphasis added).

<sup>208</sup> E-mail from Samia Nasr to Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA (Feb. 16, 2011, 10:42 AM).

<sup>209</sup> See E-mail from President, ISMP, to Dir., Div. of Medication Errors Prevention and Analysis, Off. of Surveillance and Epidemiology, CDER, FDA, et al. (Feb. 16, 2011, 2:34 PM).

<sup>210</sup> E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr (Feb. 16, 2011, 2:56 PM).

<sup>211</sup> *Id.*

<sup>212</sup> See E-mail from Reg. Operations Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr, et al. (Mar. 4, 2011, 10:12 AM).

<sup>213</sup> E-mail from Consumer Safety Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, Off. of Unapproved Drugs & Labeling Compliance (OUDLC), Off. of Compliance, CDER, FDA, to Consumer Safety Technician, OUDLC (Sept. 15, 2011, 3:46 PM). By September 2011, the Office of Compliance appears to have been restructured, resulting in the Compounding Team—formerly within the Division of New Drugs and Labeling Compliance—being renamed the Compounding and Pharmacy Practices Team within the Office of Unapproved Drugs and Labeling Compliance, Division of Prescription Drugs.

an Ameridose employee had begun. It is not clear whether this was the same informant who had spoken with NWE-DO staff on several occasions a year earlier. According to the initial NWE-DO report, the anonymous Ameridose employee stated that “when packages are dropped on the floor employees are told to pick up and ship” and that “the bubble wrap is stored directly on the floor and that this room is dirty and is never cleaned.”<sup>214</sup> The NWE-DO employee who received the complaint labeled the firm in question “Manufacturer” and marked it “Surveillance Information for Next [Establishment Inspection].”<sup>215</sup> This informant would continue to contact FDA with new concerns through mid-November, though that informant was not the only person doing so.

Based on a review of the documents, since November 2010, individuals from the California Health Department and Board of Pharmacy had been in contact with FDA’s Los Angeles District Office about concerns they had with Ameridose shipping repackaged succinylcholine, a neuromuscular blocking agent used in surgery. According to the State representatives, Ameridose was shipping the product with significantly different expiration dates than the branded product and doing so without corresponding package inserts.<sup>216</sup> The issue resurfaced in September 2011, when an employee from the Department of Public Health had asked FDA whether “Ameridose received premarket approval for the succinylcholine product” and noted that they were “concerned with microbial contamination, as well as stability of product, associated with the repackaging (from the original manufacturers) of the Ameridose products.”<sup>217</sup> These concerns were shared with Tamara Ely, the new leader of CDER’s Compounding Team, on September 28, 2011.<sup>218</sup>

One month later, the documents indicate that an anonymous Ameridose employee had also contacted FDA’s Office of Criminal Investigations regarding similar concerns as those previously raised with the NWE-DO. On October 21, 2011, Amber Wardwell, who succeeded Mutahar Shamsi as NWE-DO Compliance Branch Director, informed her colleagues that “OCI has sent over a referral for a[n] informant at Ameridose in Westboro [sic]” which involved allegations that “sales people [were] in [the] clean area filling product” and that Ameridose “continue[d] to repack Avastatin [sic] without FDA license.”<sup>219</sup> Nonetheless, CDER was steadfast in its position that it would not inspect Ameridose and investigate complaints until the compounding guidance was finalized. For example, when the District compliance officer primarily responsible for Ameridose reached out to CDER’s Compounding Team on October 24 to discuss the informant’s claims, one of the Compounding Team employees asked Tamara Ely whether she should “schedule something and let him know that we aren’t actively pursuing

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<sup>214</sup> FDA, CONSUMER COMPLAINT/INJURY REPORT, at 1 (Aug. 9, 2011).

<sup>215</sup> *Id.* at 3.

<sup>216</sup> See E-mail from Supervising Inspector, Cal. Bd. of Pharmacy, to Supervisory Consumer Safety Officer, Los Angeles Dist. Off., FDA (Nov. 18, 2010, 9:03 AM).

<sup>217</sup> E-mail from Pharmaceutical Consultant, Cal. Dep’t. of Public Health, to Supervisory Consumer Safety Officer, Los Angeles Dist. Off., FDA (Sept. 20, 2011, 9:43 AM).

<sup>218</sup> See E-mail from Tamara Ely, Team Leader, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA, to Supervisory Consumer Safety Officer, Los Angeles Dist. Off., FDA (Sept. 28, 2011, 5:51 AM).

<sup>219</sup> E-mail from Amber Wardwell, Compliance Branch Director, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (Oct. 21, 2011, 11:22 AM).

anything at this time. . . ?”<sup>220</sup> Ms. Ely responded, “I will handle it so you can focus on all things 503[A] [guidance].”<sup>221</sup> According to a subsequent email from the District compliance officer to Amber Wardwell, Ms. Ely informed the compliance officer that “CDER is in the process of drafting guidance on compounding and manufacturing” and that no inspections would be conducted until it was issued.<sup>222</sup> Ms. Ely directed the compliance officer to interview the informant and forward the notes from the interview, but acknowledged that the District Office “should not immediately follow-up but wait until the guidance is out, and then inspect as directed by CDER.” The compliance officer concluded: “*She said no compounding facility is slated to be inspected in 2012.*”<sup>223</sup>

The next day, October 25, 2011, the compliance officer had his colleague contact the informant to set up an interview, as directed by Ms. Ely. Although the informant agreed to meet with the compliance officer and several of his colleagues on October 31,<sup>224</sup> the interview was ultimately postponed until November 3 and, in the end, was brief. According to the interview notes, the informant was “concern[ed] about [the] consequences of speaking w/ FDA [in terms of] retaliation, future employment, personal safety – legal expenses if [it] goes to court, personal law suit.”<sup>225</sup> Although FDA staff agreed to look into whistleblower protections,<sup>226</sup> the Ameridose informant decided not to meet with them again after speaking with his lawyer.<sup>227</sup>

On November 17, 2011—only one day after the informant declined to meet with FDA again—the agency received an adverse event report associated with an Ameridose product. This report stated that three pregnant women who were in labor had complained of poor pain control after receiving epidural fentanyl injections subsequently determined to have been made and distributed by Ameridose. The women ultimately had C-sections.<sup>228</sup> The reporting physician or hospital pharmacist stated that they had “[n]otified [Ameridose] for investigation” and had “attempted to contact Ameridose numerous times over the last several weeks to find the outcome of the investigation.”<sup>229</sup> On January 24, 2012, FDA received an additional report associated with fentanyl produced and distributed by Ameridose. This time, the complaint related to confusing labeling resulting in “2 near misses” where nurses had stated that “they almost gave their patient’s [sic] 100mcg instead of 50mcg.”<sup>230</sup>

The next day, January 25, 2012, FDA received another report via its adverse event reporting system, this time involving a heparin product. According to the complaint, a hospital

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<sup>220</sup> E-mail Reg. Operations Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA, to Tamara Ely (Oct. 24, 2011, 9:30 AM).

<sup>221</sup> E-mail from Tamara Ely to Reg. Operations Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA (Oct. 24, 2011, 9:34 AM).

<sup>222</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Branch Director, New England Dist. Off., FDA (Oct. 24, 2011, 10:07 AM).

<sup>223</sup> *Id.* (emphasis added).

<sup>224</sup> Notes of Investigator, New England Dist. Off., FDA (Oct. 25, 2011, 9:30 AM).

<sup>225</sup> Notes of Investigator, New England Dist. Off., FDA (Nov. 3, 2011, 3:00 PM).

<sup>226</sup> *See id.*

<sup>227</sup> E-mail from Supervisory Consumer Safety Officer, New England Dist. Off., FDA, to Chris van Twuyver, Dir., Investigations Branch, New England Dist. Off., FDA (Nov. 16, 2011, 4:10 PM).

<sup>228</sup> *See* FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (Nov. 17, 2011).

<sup>229</sup> *Id.*

<sup>230</sup> FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (Jan. 24, 2012).

"had a patient that the doctor had ordered a Heparin drip for. The patient had a bag and the labs came back that their level had not changed. They increased the drip and rechecked labs [and] still no change. They changed the bag [and followed the] same processes and still not level. Pharmacy had lab test the . . . 2 bags . . . and neither bag had any Heparin in [it]. These bags were made by Ameridose, a compounding pharmacy in Framingham, MA."<sup>231</sup>

On March 12, 2012, another adverse event report was submitted to FDA, again involving potency issues with pain medications produced by Ameridose. Again, according to the complaint, "Ameridose was contacted about the potential problem and is conducting an investigation."<sup>232</sup> Less than two weeks later, on March 23, 2012, FDA received yet another report involving another "Hospital Close-call" associated with confusing Ameridose labeling.<sup>233</sup>

No other documents or communications related to this five-month string of adverse event reports associated with Ameridose products were produced to the Committee, suggesting that FDA did not take any further steps to investigate them, let alone re-inspect the company's facilities. Based on the MDPH's assertion to Committee staff, none of these complaints were forward to the State either.

On May 24, 2012, one of the inspectors from the NWE-DO who had previously visited Ameridose was contacted by a special agent in FDA's OCI. According to notes from the call, the agent was "interested in setting up [a] meeting to discuss Ameridose."<sup>234</sup> The inspector then emailed a supervisor in the District Office informing her that "[OCI] had recently received a complaint for Ameridose" and that the agent "would like to set up a time to meet with me to discuss what I saw at the firm and ask a few other questions about our inspection there."<sup>235</sup> The compliance officer primarily responsible for Ameridose informed his contact at CDER about the request, who replied by copying Pamela Lee—"the new [Team Leader] for the compounding team."<sup>236</sup> It is apparent from the documents that a teleconference was scheduled and ultimately occurred on June 5, 2012. Representatives from OCI, CDER, and the NWE-DO participated.<sup>237</sup> Based on notes from the call, the "anonymous complaint" that generated the discussion was "from HHS [U.S. Department of Health and Human Services] IG" and involved "drugs [being] misbranded, [and] not complying with GMPs."<sup>238</sup> The notes also indicate that Ms. Lee informed the group that CDER was "revising guidelines so enforcement actions [were] on hold unless [there was] clear harm or fraud."<sup>239</sup> After the call, Pamela Lee followed up with one of the participating NWE-DO compliance officers about the discussion. She asked what the compliance officer "meant when [she] said Ameridose did not have patient-specific prescriptions

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<sup>231</sup> *Id.*

<sup>232</sup> FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (Jan. 25, 2012).

<sup>233</sup> FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (Mar. 23, 2012).

<sup>234</sup> Notes of Investigator, New England Dist. Off., FDA (May 24, 2012, 1:20 PM).

<sup>235</sup> E-mail from Investigator, New England Dist. Off., FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA (May 24, 2012, 10:01 AM).

<sup>236</sup> E-mail from Reg. Operations Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (May 29, 2012, 9:58 AM).

<sup>237</sup> See Notes of Investigator, New England Dist. Off., FDA (June 5, 2012).

<sup>238</sup> *Id.*

<sup>239</sup> *Id.*

for approximately 99% of their drugs but instead had ‘physician orders.’<sup>240</sup> The compliance officer responded by clarifying that aside from certain dialysis patients, “The[re] are no patient/physician orders. There is nothing signed by MD’s except for the dialysis orders.”<sup>241</sup>

It is unclear from the documents whether anything associated with the underlying complaint that had been raised with HHS IG was resolved prior to the meningitis outbreak beginning in late September 2012. However, on July 17, 2012, after the NWE-DO was informed of NECC violating the Colorado Cease and Desist Order, the District compliance officer primarily responsible for NECC informed his colleague about the news and stated that “CDER said last year we may do something at the end of this year with compounding pharmacies. I recently had a meeting with OCI based on a complaint they received and they may be doing something with Ameridose. I invited CDER to the meeting and they were on the speakerphone. They did not want us going to the firm.”<sup>242</sup> The compliance officer then forwarded the information received from FDA’s Denver District Office to Pamela Lee and asked, “Based on past conversations that we may start enforcing compounding pharmacies at the end of this year do you want us to wait until you issue an assignment to go to [NECC]?”<sup>243</sup> Ms. Lee’s reply, if there was one, was not produced to the Committee.

At this point in time, NECC had already shipped two of the three batches of fatal methylprednisolone acetate to facilities across the country. The meningitis outbreak started to unfold in late September. After it was determined that NECC was the responsible entity, FDA initiated an inspection of the facility, along with the State, on September 26, 2012. On October 10, 2012 FDA and the State began an inspection of Ameridose because, according to FDA, “Ameridose and NECC of Framingham, Mass. share some of the same managers.”<sup>244</sup>

Prior to the inspection of Ameridose, on October 5, 2012, the NWE-DO received a new complaint from an anonymous employee at Ameridose. According to the report, the informant stated that, approximately one year ago, NECC had received a large order for a product used to prevent nausea and vomiting associated with chemotherapy. He explained that since NECC did not have the capacity to fill this order, “a couple batches containing a couple thousand syringes were produced at Ameridose for NECC” and that “it wasn’t documented because it was not supposed to be done this way and illegal.” According to the NWE-DO report, the informant concluded by stating that “the same people that own NECC also own Ameridose” and that the informant was “instructed by management to keep quiet as Ameridose does not want to be associated with NECC.”<sup>245</sup>

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<sup>240</sup> E-mail from Pamela Lee, Senior Regulatory Operations Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (June 5, 2011, 3:21 PM).

<sup>241</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Pamela Lee (June 5, 2011, 3:34 PM).

<sup>242</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (July 17, 2012, 8:19 AM).

<sup>243</sup> E-mail from Compliance Officer, New England Dist. Off., FDA, to Pamela Lee, et al. (July 17, 2012, 8:35 AM).

<sup>244</sup> FDA, *Questions and Answers on Ameridose Recall* (Nov. 1, 2012) [hereinafter, “Ameridose Q&A”], available at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm326471.htm>.

<sup>245</sup> FDA, CONSUMER COMPLAINT/INJURY REPORT (Oct. 5, 2012).

On November 1, 2012, FDA announced that Ameridose was conducting a voluntary recall of all of its unexpired products in circulation based on “the preliminary results of the FDA’s ongoing inspection, which has raised concerns for the FDA about a lack of sterility assurance. . . .”<sup>246</sup> On November 9, 2012, FDA issued Gregory Conigliaro a Form 483, documenting the agency’s observations during the inspection of Ameridose beginning on October 10.<sup>247</sup> The observations included in this twenty-page document are too numerous to address in this memorandum. In summarizing the document, one FDA spokesperson stated that the firm “fails to test finished product for potency, failed to investigate complaints for ineffective products, failed to investigate violations of their own environmental sampling plan and fails to adequately maintain equipment and facilities used to manufacture sterile drug products.”<sup>248</sup> For more reasons than one, this statement does not even begin to tell the whole story.

#### PART V: CONCLUSION

It can and should be stipulated that the fungal meningitis outbreak would not have occurred if not for a company whose management was willing to consistently cut corners and prioritize the expansion of their business over the safety of their products. That being said, NECC was not operating in the shadows. NECC had been on FDA’s radar since 2002 and never left.

One of FDA’s fundamental reasons for existence is to protect the public health by assuring the safety of our nation’s drug supply. With respect to NECC and Ameridose, documents produced to the Committee raise serious questions about whether FDA repeatedly failed in its core mission. The documents also indicate that it was by sheer chance that NECC products caused these deaths and illnesses, as opposed to products produced and distributed by Ameridose. FDA employees were well aware of the link between these two companies. The agency’s inaction in the face of years of complaints and red flags associated with the safety of both companies’ products and underlying practices had a tragic ending. While nobody could have fully anticipated the scope of this terrible outbreak, FDA was on notice that something like this might occur.

Issues with the safety of NECC and Ameridose products and practices aside, by 2012 FDA had a deep understanding of the nature and scope of the companies’ business; the agency knew that both NECC and Ameridose were engaged in activities that strongly suggested they were operating as drug manufacturers. Had the companies long ago crossed any line FDA could conceivably have drawn in the sand to differentiate pharmacy compounding from drug manufacturing? Even if FDA was so unsure of its authority to initiate enforcement actions against these companies after the Circuit Court split, was there anything in the law that precluded them from informing the State about the litany of complaints the agency had independently

<sup>246</sup> FDA, Ameridose Q&A, *supra* note 244.

<sup>247</sup> See FDA, AMERIDOSE, LLC, FORM FDA 483, available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM327729.pdf>.

<sup>248</sup> Elizabeth Weise, *FDA finds contamination at Ameridose*, USA Today, Nov. 13, 2012, available at <http://www.usatoday.com/story/news/nation/2012/11/12/fda-ameridose-meningitis/1700589/>.

received about NECC and Ameridose and strongly encouraging State action for the sake of patients across the country?

The Committee is committed to ensuring that something like this never happens again. If additional legislation is needed so FDA can adequately enforce the pertinent provisions of the FDCA with respect to companies that label themselves compounding pharmacies, yet are engaged in large-scale manufacturing and distribution activities, the Committee will work on such legislation. That being said, additional authority will not necessarily solve the fundamental issues within FDA that allowed this tragedy to unfold right under the agency's nose. Guidance documents will always need to be updated. Clarifying regulations will always need to be drafted. Statutory authority will always need to be defended. How many complaints, red flags, and close calls does FDA need to accumulate before protecting the public health outweighs any of these other activities?